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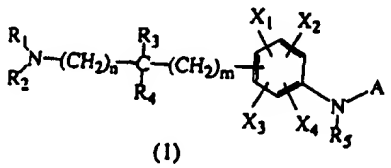
(54) AROMATIC AMINE DERIVATIVES HAVING NOS INHIBITORY EFFECT

(57) Compounds represented by the general formula (1):



(1)

(where R_1 and R_2 are typically a hydrogen atom; R_3 and R_4 are typically a hydrogen atom or a lower alkyl group; R_5 is typically a hydrogen atom; X_1, X_2, X_3 and X_4 are typically a hydrogen atom or a lower alkoxy group; A is typically an optionally substituted pyridine ring; m and n are each 0 or 1) have an NOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases and other pharmaceuticals.

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Description

TECHNICAL FIELD

[0001] This invention relates to N-substituted aniline derivatives, more particularly to compounds represented by the general formula (I) that have a nitric oxide synthase (NOS) inhibiting action to suppress the production of nitric oxide (NO) and thereby prove effective against disorders and diseases in which excessive NO or NO metabolites are supposedly involved, namely, cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothromobotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus. The invention also relates to possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof. The invention further relates to preventives and therapeutics that contain said compounds, derivatives or pharmaceutically acceptable salts as active ingredients.

BACKGROUND ART

[0002] The number of deaths from cerebrovascular diseases in Japan had increased until 1970 when it began to decline mostly due to the improvement in their acute-phase therapy. Nevertheless, cerebrovascular diseases remain the second leading cause of death among adult diseases, next only to cancers. As for the incidence of cerebrovascular diseases, many statistical surveys indicate that it is generally constant and in view of the fact that the number of elderly persons will increase at an uncomparably faster speed in Japan than any other country in the world, the number of patients suffering from cerebrovascular diseases is estimated to increase rather than decrease in the future. The declining mortality and the growing population of aged people combine to increase the cases of cerebrovascular diseases in the chronic phase and this has presented with a national problem not only from the aspects of individual patients and society at large but also from the viewpoint of medical economics since patients with chronic cerebrovascular disease are inevitably involved in long-term care. In cerebral infarction that accounts for most cases of cerebrovascular diseases, cerebral arteries are occluded and blood deficit starting at the blocked site extends to the peripheral site, causing an ischemic state. The symptoms of cerebral infarction in the chronic phase are in almost all cases derived from the loss of neurons and it would be extremely difficult to develop medications or established therapeutic methods for achieving complete recovery from those symptoms. Therefore, it is no exaggeration that the improvement in the performance of treatments for cerebral infarction depends on how patients in an acute phase can be treated with a specific view to protecting neurons and how far their symptoms can be ameliorated in the acute phase. However, most of the medications currently in clinical use are antiplatelet drugs, anticoagulants and thrombolytics and none of these have a direct nerve protecting action (see Kazuo MINEMATSU et al., "MEDICINA", published by Igaku Shoin, 32, 1995 and Hidehiro MIZUSAWA et al., published by Nankodo, "Naika" 79, 1997). Therefore, it is desired to develop a drug that provides an effective therapy for cerebrovascular diseases, in particular cerebral infarction, by working in an entirely novel and different mechanism of action from the conventional medications.

[0003] A presently dominant theory based on genetic DNA analyses holds that NOS exists in at least three isoforms, namely, calcium-dependent nNOS (type 1) which is present constitutively in neurons, calcium-dependent eNOS (type 3) which is present constitutively in vascular endothelial cells, and apparently calcium-independent iNOS (type 2) which is induced and synthesized by stimulation with cytokines and/or lipopolysaccharides (LPS) in macrophages and many other cells (Nathan et al., FASEB J. 16, 3051-3064, 1992; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0004] A mechanism that has been proposed as being most probable for explaining the brain tissue damage which accompanies cerebral ischemia is a pathway comprising the sequence of elevation in the extracellular glutamic acid level, hyperactivation of glutamic acid receptors on the post-synapses, elevation in the intracellular calcium level and activation of calcium-dependent enzymes (Siesjö, J. Cereb. Blood Flow Metab. 1, 155-185, 1981; Siesjö, J. Neurosurg. 60, 883-908, 1984; Choi, Trends Neurosci. 11, 465-469, 1988; Siesjö and Bengstsson, J. Cereb. Blood Flow Metab. 9, 127-140, 1989). As already mentioned, nNOS is calcium-dependent, so the inhibition of hyperactivation of this type of NOS isoforms would contribute to the neuro-protective effects of NOS inhibitors (Dawson et al., Annals Neurol. 32, 297-311, 1992).

[0005] As a matter of fact, the mRNA level of nNOS and the number of nNOS containing neurons start to increase early after focal cerebral ischemia in rats and their temporal alterations coincide with the development of infarction (Zhang et al., Brain Res. 654, 85-95, 1994). In addition, in a mouse model of focal cerebral ischemia, the percent inhibition of nNOS activity and the percent reduction of infarct volume correlate to each other at least in a dose range of N^G-nitro-L-arginine (L-NA) that produces a recognizable infarct volume reductive action (Carreau et al., Eur. J. Pharmacol. 256, 241-249, 1994). Further in addition, it has been reported that in nNOS knockout mice, the infarct volume

observed after focal cerebral ischemia is significantly smaller than that in the control (Huang et al., Science 265, 1883-1085, 1994).

[0006] Referring now to NO, it is at least one of the essences of endothelium-derived relaxing factor (EDRF) and, hence, is believed to take part in the adjustment of the tension of blood vessels and the blood flow (Moncade et al., Pharmacol. Rev. 43, 109-142, 1991). As a matter of fact, it was reported that when rats were administered high doses of L-NA, the cerebral blood flow was found to decrease in a dose-dependent manner as the blood pressure increased (Toru MATSUI et al., Jikken Igaku, 11, 55-60, 1993). The brain has a mechanism by which the cerebral blood flow is maintained at a constant level notwithstanding the variations of blood pressure over a specified range (which is commonly referred to as "autoregulation mechanism") ("NOSOTCHU JIKKEN HANDBOOK", complied by Keiji SANO, published by IPC, 247-249, 1990). The report of Matsui et al. suggests the failure of this "autoregulation mechanism" to operate. Therefore, if eNOS is particularly inhibited beyond a certain limit in an episode of brain ischemia, the cerebral blood flow will decrease and the blood pressure will increase, thereby aggravating the dynamics of microcirculation, possibly leading to an expansion of the ischemic lesion. It was also reported that in eNOS knockout mice, the infarct observed after focal cerebral ischemia was larger than that in the control but could be reduced significantly by administration of L-NA (Huang et al., J. Cereb. Blood Flow Metab. 16, 981-987, 1996). These reports show that eNOS-derived NO probably works protectively on the brain tissue through the intermediary of a vasodilating action, a platelet aggregation suppressing action and so forth.

[0007] The present inventors previously found that L-NA, already known to be a NOS inhibitor, possessed ameliorative effects on the brain edema and cerebral infarction following phenomena that developed after experimental cerebral ischemia (Nagafuji et al., Neurosci. Lett. 147, 159-162, 1992; Japanese Patent Public Disclosure No. 192080/1994), as well as necrotic neuronal cell death (Nagafuji et al., Eur. J. Pharmacol. Env. Tox. 248, 325-328, 1993). On the other hand, relatively high doses of NOS inhibitors have been reported to be entirely ineffective against ischemic brain damage and sometimes aggravating it (Idadecola et al., J. Cereb. Blood Flow Metab. 14, 175-192, 1994; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995). It should, however, be stressed that as a matter of fact, all papers that reported the changes of NO or NO-related metabolites in the brain and blood in permanent or temporary cerebral ischemic models agreed in their results to show the increase in the levels of those substances (Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0008] One of the reasons for explaining the fact that conflicting reports have been made about the effectiveness of NOS inhibitors in cerebral ischemic models would be the low selectivity of the employed NOS inhibitors for nNOS. As a matter of fact, no existing NOS inhibitors including L-NA and N^G-nitro-L-arginine methyl ester (L-NAME) have a highly selective inhibitory effect on a specific NOS isoform (Nagafuji et al. Neuroreport 6, 1541-1545, 1995; Nagafuji et al. Mol. Chem. Neuropathol. 26, 107-157, 1995). Therefore, it may well be concluded that desirable therapeutics of ischemic cerebrovascular diseases should have a selective inhibitory effect on nNOS (Nowicki et al., Eur. J. Pharmacol. 204, 339-340, 1991; Dawson et al., Proc. Natl. Acad. Sci. USA 88, 6368-6371, 1991; Iadecola et al., J. Cereb. Blood Flow Metab. 15, 52-59, 1995; Iadecola et al., J. Cereb. Blood Flow Metab. 15, 378-384, 1995; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0009] It has also been suggested that nNOS inhibitors have the potential for use as therapeutics of traumatic brain injuries (Oury et al., J. Biol. Chem. 268, 15394-15398, 1993; MacKenzie et al., Neuroreport 6, 1789-1794, 1995; Mesenge et al., J. Neurotrauma. 13, 11-16, 1996; Wallis et al., Brain Res., 710, 169-177, 1996), headache and other pains (Moore et al., Br. J. Pharmacol. 102, 198-202, 1991; Olesen., Trends Pharmacol. 15, 149-153, 1994), Parkinson's disease (Youdim et al., Advances Neurol. 60, 259-266, 1993; Schulz et al., J. Neurochem. 64, 936-939, 1995; Hantraye et al., Nature Medicine 2, 1017-1021, 1996), Alzheimer's disease (Hu and El-FaKahany, Neuroreport 4, 760-762, 1993 Meda et al., Nature 374, 647-650, 1995), seizure (Rigaud-Monnet et al., J. Cereb. Blood Flow Metab. 14, 581-590, 1994), and morphine tolerance and dependence (Kolesnikov et al., Eur. J. Pharmacol. 221, 399-400, 1992; Cappendijk et al., Neurosci. Lett. 162, 97-100, 1993).

[0010] Upon stimulation by certain kinds of cytokines and/or LPS, iNOS is induced in immunocytes such as macrophages and glial cells and other cells, and the resulting large amount of NO will dilate blood vessels to cause a fatal drop in blood pressure. Therefore, it is speculated that an iNOS inhibitor may be effective against septic shocks (Kilbourn and Griffith, J. Natl. Cancer Inst. 84, 827-831, 1992; Cobb et al., Crit. Care Med. 21, 1261-1263, 1993; Lorente et al., Crit. Care Med. 21, 1287-1295, 1993). Further, it has been suggested that iNOS inhibitors are useful as therapeutics of chronic rheumatoid arthritis and osteoarthritis (Farrell et al., Ann, Rheum. Dis. 51, 1219-1222, 1992; Hauselmann et al., FEBS Lett. 352, 361-364, 1994; Islante et al., Br. J. Pharmacol. 110, 701-706, 1993), viral or nonviral infections (Zembvitz and Vane, Proc. Natl. Acad. Sci. USA 89, 2051-2055, 1992; Koprowski et al., Proc. Natl. Acad. Sci. USA 90, 3024-3027, 1993) and diabetes mellitus (Kolb et al., Life Sci. PL213-PL217, 1991).

[0011] The NOS inhibitors so far reported to have a certain degree of selectivity for nNOS are N^G-cyclopropyl-L-arginine (L-CPA)(Lamberte et al., Eur. J. Pharmacol. 216, 131-134, 1992), L-NA (Furfine et al., Biochem. 32, 8512-8517, 1993), S-methyl-L-thiocitrulline (L-MIN) (Narayanan and Griffith, J. Med. Chem. 37, 885-887, 1994; Furfine et al.,

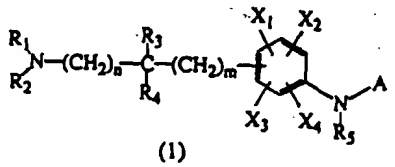
J. Biol. Chem. 37, 885-887, 1994; Furfine et al. J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995; Nagafuji et al., Neuroreport 6, 1541-1545, 1995), S-ethyl-L-thiocitrulline (L-EIN) (Furfine et al., J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al.,J. Biol. Chem. 270, 11103-11110, 1995), and ARL 17477 (Gentile et al., WO95/05363; Zhang et al., J. Cereb. Blood Flow Metab., 16, 599-604, 1996).

[0012] In addition, the inhibitors that have been reported to have a certain degree of selectivity for iNOS are N^G-iminoethyl-L-ornithine (L-NIO) (McCall et al., Br. J. Pharmacol. 102, 234-238, 1991) and aminoguanidine (AG) (Griffith et al., Br. J. Pharmacol. 110, 963-968, 1993; Hasan et al. Eur. J. Pharmacol. 249, 101-106, 1993).

DISCLOSURE OF INVENTION

[0013] An object of the present invention is to provide novel compounds that have an inhibitory effect on calcium-dependent nNOS which is present constitutively in the brain, particularly in neurons or an inducible and apparently calcium-independent iNOS and which are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

[0014] As a result of the intensive studies made in order to attain the stated object, the present inventors found that aromatic amine derivatives represented by the general formula (I), or possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof have an inhibitory action on type 1 NOS and so forth, thereby exhibiting marked effectiveness as therapeutics of cerebrovascular diseases (especially as therapeutics of occlusive cerebrovascular diseases):



(1)

(where R_1 and R_2 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxycarbonyl group, or R_1 and R_2 may combine together to form a 3- to 8-membered ring;

R_3 and R_4 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms;
R_5 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;
X_1, X_2, X_3, and X_4, which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=O)X_7$;
where X_5 and X_6 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring;
X_7 is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX_8X_9;
where X_8 and X_9 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_8 and X_9 may combine together to form a 3- to 8-membered ring;
A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;
n and m are each an integer of 0 or 1).

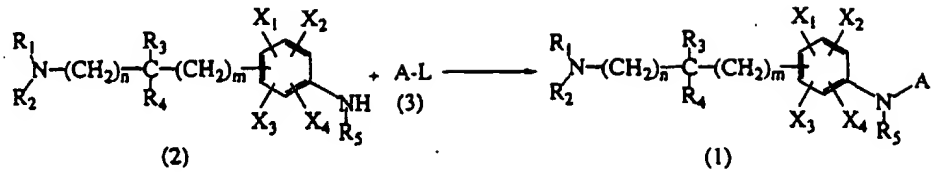
[0015] The present invention has been accomplished on the basis of this finding.

[0016] The present invention also provides a process for producing a compound of the general formula (1) which is

represented by the reaction pathway (A):

Reaction pathway (A)

[0017]



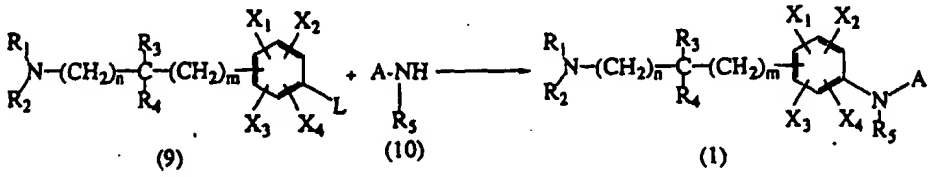
(2) (3) (1)

namely, a process in which a substituted aniline represented by the general formula (2) (where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, n and m have the same meanings as defined above; R_5 is a hydrogen atom or an optionally substituted lower alkyl group) is reacted with a compound represented by the general formula (3) (where A has the same meaning as defined above; L is a leaving group) to produce a compound represented by the general formula (1).

[0018] The present invention further provides a process for producing a compound of the general formula (1) which is represented by the reaction pathway (B):

Reaction pathway (B)

[0019]



(9) (10) (1)

namely, a process in which a substituted benzene represented by the general formula (9) (where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, L, n and m have the same meanings as defined above) is reacted with a compound represented by the general formula (10) (where A and R_5 have the same meanings as defined above) to produce a compound represented by the general formula (1).

BEST MODE FOR CARRYING OUT THE INVENTION

[0020] In the present invention, the 5- or 6-membered aromatic hetero ring as an example of A which contains at least one nitrogen atom as a hetero atom may be exemplified by a pyrrole ring, a pyrrole-1-oxide ring, a pyrazole ring, a pyrazole-1-oxide ring, a pyrazole-2-oxide ring, a pyrazole-1,2-dioxide ring, an imidazole ring, an imidazole-1-oxide ring, an imidazole-3-oxide ring, an imidazole-1,3-dioxide ring, an isoxazole ring, an isoxazole-2-oxide ring, an oxazole ring, an oxazole-3-oxide ring, an isothiazole ring, an isothiazole-1-oxide ring, an isothiazole-1,1-dioxide ring, an isothiazole-1,2-dioxide ring, an isothiazole-2-oxide ring, a thiazole ring, a thiazole-1-oxide ring, a thiazole-1,1-dioxide ring, a thiazole-3-oxide ring, a pyridine ring, a pyridine-N-oxide ring, a pyridazine ring, a pyridazine-1-oxide ring, a pyridazine-1,2-dioxide ring, a pyrimidine ring, a pyrimidine-1-oxide ring, a pyrimidine-1,3-dioxide ring, a pyrazine ring, a pyrazine-1-oxide ring or a pyrazine-1,4-dioxide ring or the like;

the substituent in A is a hydroxyl group, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a lower alkoxy group, a lower alkyl group, a lower alkylthio group, $NX_{10}X_{11}$ or $C(=O)X_{12}$;
where X_{10} and X_{11} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_{10} and X_{11} may combine

together to form a 3- to 8-membered ring;

X_{12} is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group or $NX_{13}X_{14}$;

where X_{13} and X_{14} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_{13} and X_{14} may combine together to form a 3- to 8-membered ring;

the lower alkyl group is a straight-chained alkyl group having 1 - 6 carbon atoms, or a branched or cyclic alkyl group having 3 - 8 carbon atoms and may be exemplified by a methyl group, an ethyl group, an n-propyl group, an n-butyl group, an n-pentyl group, an n-hexyl group, an i-propyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an i-pentyl group, a neopentyl group, a t-pentyl group, an i-hexyl group, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group or a cyclooctyl group or the like;

the lower alkenyl group is a straight-chained alkenyl group having 2 - 6 carbon atoms or a branched alkenyl group having 3 - 6 carbon atoms and may be exemplified by a vinyl group, an allyl group, a 1-butenyl group, a 1-pentenyl group, a 1-hexenyl group, a 2-butenyl group, a 2-pentenyl group, a 2-hexenyl group, an isopropenyl group, a 2-butenyl group or a 1-methyl-1-propenyl group or the like;

the lower alkynyl group is a straight-chained alkynyl group having 2 - 6 carbon atoms or a branched alkynyl group having 3 - 6 carbon atoms and may be exemplified by an ethynyl group, a 1-propynyl group, a 1-butynyl group, a 1-pentynyl group, a 1-hexynyl group, a 2-propynyl group, a 2-butynyl group, a 2-pentynyl group, a 2-hexynyl group, a 1-methyl-2-propynyl group, a 3-methyl-1-butynyl group or a 1-ethyl-2-propynyl group or the like;

the lower alkoxy group is a straight-chained alkoxy group having 1 - 6 carbon atoms or a branched or cyclic alkoxy group having 3 - 8 carbon atoms and may be exemplified by a methoxy group, an ethoxy group, an n-propoxy group, an n-butoxy group, an n-pentoxy group, an n-hexoxy group, an i-propoxy group, an i-butoxy group, a sec-butoxy group, a t-butoxy group, an i-pentoxy group, a neopentoxy group, a t-pentoxy group, an i-hexoxy group, a cyclopropoxy group, a cyclobutoxy group, a cyclopentoxy group, a cyclohexoxy group, a cycloheptoxy group or a cyclooctoxy group or the like;

the lower alkylthio group is a straight-chained alkylthio group having 1 - 6 carbon atoms or a branched or cyclic alkylthio group having 3 - 8 carbon atoms and may be exemplified by a methylthio group, an ethylthio group, an n-propylthio group, an n-butylthio group, an n-pentylthio group, an n-hexylthio group, an i-propylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, an i-pentylthio group, a neopentylthio group, a t-pentylthio group, an i-hexylthio group, a cyclopropylthio group, a cyclobutylthio group, a cyclopentylthio group, a cyclohexylthio group, a cycloheptylthio group or a cyclooctylthio group or the like;

the acyl group is not only a formyl group but also an alkylcarbonyl group the alkyl portion of which is a lower alkyl group, as well as an arylcarbonyl group and may be exemplified by an acetyl group, a propionyl group, a butyryl group, a valeryl group, an isobutyryl group, an isovaleryl group, a pivaloyl group, a benzoyl group, a phthaloyl group or a toluoyl group or the like;

the lower alkoxycarbonyl group is an alkoxycarbonyl group the alkyl portion of which is a lower alkyl group and may be exemplified by a methoxycarbonyl group, an ethoxycarbonyl group, an n-propoxycarbonyl group, an n-butoxycarbonyl group, an n-pentoxycarbonyl group, an n-hexoxycarbonyl group, an i-propoxycarbonyl group, an i-butoxycarbonyl group, a sec-butoxycarbonyl group, a t-butoxycarbonyl group, an i-pentoxycarbonyl group, a neopentoxycarbonyl group, a t-pentoxycarbonyl group, an i-hexoxycarbonyl group, a cyclopropoxycarbonyl group, a cyclobutoxycarbonyl group, a cyclopentoxycarbonyl group, a cyclohexoxycarbonyl group, a cycloheptoxycarbonyl group, or a cyclooctoxycarbonyl group or the like;

the halogen atom is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom;

the leaving group is a halogen atom, a trifluoromethanesulfonyloxy group, a p-toluenesulfonyloxy group or a methanesulfonyloxy group;

the substituent in the case where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, or X_{14} is an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group or an optionally substituted lower alkoxycarbonyl group may be exemplified by a halogen atom, a phenyl group optionally substituted by a halogen atom or a lower alkyl group or a cyclic alkyl group having 3 - 8 carbon atoms;

the ring as the 3- to 8-membered ring optionally formed by R_1 and R_2 taken together, the ring as the 3- to 8-membered ring optionally formed by X_5 and X_6 taken together, the ring as the 3- to 8-membered ring optionally formed by X_8 and X_9 taken together, the ring as the 3- to 8-membered ring optionally formed by X_{10} and X_{11} taken together, and the ring as the 3- to 8-membered ring optionally formed by X_{13} and X_{14} taken together are each a hetero ring containing at least one nitrogen atom as a hetero atom and may be exemplified by a pyrrole ring, a pyrazole ring, an imidazole ring, a triazole ring, an aziridine ring, an azetidine ring, a pyrrolidine ring, a piperidine ring, a piperazine ring, a morpholine ring, a thiomorpholine ring, an azepane ring or an azocane ring or the like;

the ring as the monocyclic or fused ring having 3 - 10 carbon atoms that is optionally formed by R_3 and R_4 taken together may be exemplified by a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring,

a cycloheptane ring, a cyclooctane ring, an indane ring or a tetralin ring or the like;

NX_5X_6, NX_8X_9, $NX_{10}X_{11}$, and $NX_{13}X_{14}$ may be exemplified by an amino group, a methylamino group, a benzylamino group, an ethylamino group, a dimethylamino group, an ethylmethylamino group, a pyrrolidine-1-yl group, a piperidine-1-yl group, a morpholine-4-yl group, an acetamido group, a benzamido group, an N-methylacetamide group, a benzamido group, a tert-butoxycarbonylamino group, an N-methyl-t-butoxycarbonyl-amino group, a pyrrole-1-yl group, a pyrazole-1-yl group, an imidazole-1-yl group, a triazole-1-yl group, an aziridine-1-yl group, an azetidine-1-yl group, a pyrrolidine-1-yl group, a piperidine-1-yl group, a piperazine-1-yl group, a morpholine-4-yl group or a thiomorpholine-4-yl group or the like;

$C(=O)X_7$ may be exemplified by a formyl group, a carboxyl group, an acetyl group, a propionyl group, a cyclobutyryl group, a methoxycarbonyl group, an ethoxycarbonyl group, a t-butoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, an N-ethylcarbamoyl group, an N,N-dimethylcarbamoyl group, an N-ethyl-N-methylcarbamoyl group, a pyrrolidinecarbonyl group, a piperidinecarbonyl group or a morpholinecarbonyl group or the like;

R_1 and R_2 are preferably a hydrogen atom;

R_3 and R_4 are preferably a hydrogen atom, a lower alkyl group having 1 - 3 carbon atoms or a monocyclic ring having 3 - 5 carbon atoms, with a hydrogen atom, a methyl group, an ethyl group or a cyclobutyl group being particularly preferred;

R_5 is preferably a hydrogen atom;

X_1, X_2, X_3, and X_4 are preferably a hydrogen atom, a halogen atom, a lower alkyl group having 1 - 3 carbon atoms or a lower alkoxy group having 1 - 3 carbon atoms, with a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, a methoxy group, an ethyoxy group or an n-propoxy group being particularly preferred;

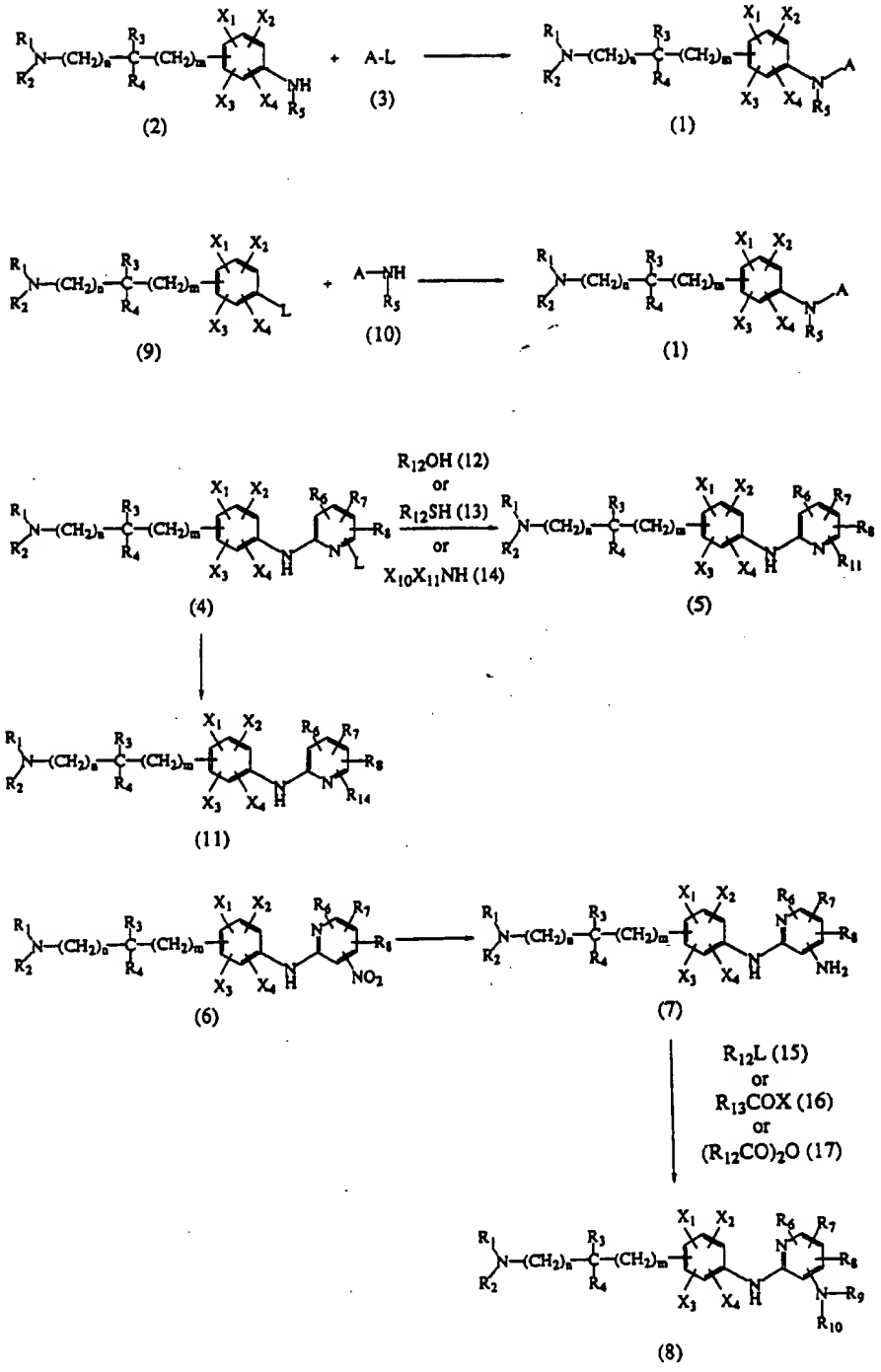
A is preferably an optionally substituted benzene or pyridine ring, and more preferred is a benzene or pyridine ring that is substituted by a nitro group, a lower alkyl group having 1 - 3 carbon atoms, a lower alkoxy group having 1 - 3 carbon atoms or a lower alkylthio group having 1 - 3 carbon atoms, with a 6-methoxy-3-nitrobenzene-2-yl group, a 6-methyl-3-nitropyridine-2-yl group, a 6-methoxy-3-nitro-pyridine-2-yl group or a 4-methylpyridine-2-yl group being particularly preferred;

m and n are such that if they are both zero, the substituents other than X_1, X_2, X_3, and X_4 are preferably meta-substituted on the benzene nucleus whereas if $m + n = 1$, the substituents other than X_1, X_2, X_3, and X_4 are preferably ortho- or para-substituted on the benzene nucleus.

[0021] Preferred compounds represented by the general formula (1) are 2-(3-aminomethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-3-ethyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-ethoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitrobenzene, 2-(3-aminomethylphenylamino)-6-methoxy-3-nitrobenzene, 2-(3-aminomethyl-2-methylphenylamino)-6-methoxy-3-nitropyridine, 2-(4-aminoethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-fluorophenylamino)-6-methoxy-3-nitro-pyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethoxyphenylamino)-4-methylpyridine, 2-(2-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-chlorophenylamino)-4-methylpyridine, 2-(3-(1-amino-cyclobutyl)phenylamino)-4-methylpyridine, 2-(4-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chlorophenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-(n-propoxy)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chloro-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-4-methylpyridine and 2-(3-aminomethyl-2-(i-propoxy)phenylamino)-4-methylpyridine.

[0022] In addition to the compounds represented by the general formula (1), the present invention also encompasses their possible tautomers, stereoisomers, optionally active forms and mixtures thereof.

[0023] The compounds of the invention which are represented by the general formula (1) may typically be synthesized by the following schemes:



[0024] The compound represented by the general formula (1) can be synthesized by reacting a compound of the general formula (2), used as a starting material, with a compound of the general formula (3).

[0025] In the general formulas (1), (2) and (3), R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, A, L, n and m

each have the same meanings as defined above.

[0026] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (2) with the compound of the general formula (3) in the presence of a base such as potassium carbonate, triethylamine, diisopropylethylamine, potassium t-butoxide or sodium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphophinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or 1,4-dioxane, at a temperature between room temperature and the boiling point of the reaction mixture. Preferably synthesis can be made by performing the reaction in the presence of triethylamine or diisopropylethylamine in dimethylformamide at 60°C or by performing the reaction in the presence of potassium carbonate, potassium t-butoxide or sodium t-butoxide, with a palladium catalyst and a ligand diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl added, in acetonitrile or toluene at a temperature between 80°C and the boiling point of the reaction mixture.

[0027] The compound represented by the general formula (1) can also be synthesized by reacting a compound of the general formula (9), used as a starting material, with a compound of the general formula (10).

[0028] In the general formulas (1), (9) and (10), R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, R_5, A, L, m and n each have the same meanings as defined above.

[0029] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (9) with the compound of the general formula (10) in the presence of a base such as potassium carbonate, triethylamine, potassium t-butoxide or sodium t-butoxide, preferably in the presence of potassium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphosphinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, preferably a palladium catalyst and a ligand diphenylphosphinoferrocene being added, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or dioxane, preferably in toluene, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at 80°C.

[0030] Among the compounds represented by the general formula (1), one which is represented by the general formula (5) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$ can also be synthesized starting with a compound of the general formula (4) with the leaving group attached.

[0031] In the general formulas (4), (5), (12), (13) and (14),

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, L, m and n each has the same meanings as defined above;
R_6 is an electron withdrawing group such as a nitro group, a cyano group, a trifluoromethyl group or $C(=O)X_7$;
R_7 and R_8 are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a hydroxyl group, a lower alkoxy group, a lower alkyl group, a lower alkylthio group, NX_5X_6 or $C(=O)X_7$;
where X_5, X_6, and X_7 each has the same meanings as defined above;
R_{11} is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$;
R_{12} and X_{10} are each a lower alkyl group;
X_{11} is a hydrogen atom or a lower alkyl group.

[0032] Stated more specifically, the compound represented by the general formula (5) can also be synthesized from the compound of the formula (4) by desirably reacting it with a corresponding compound of the general formula (12), (13) or (14) in the presence of a base such as triethylamine or sodium hydride in a solvent inert to the reaction such as dimethylformamide, tetrahydrofuran or acetonitrile at a temperature between room temperature and the boiling point of the reaction mixture.

[0033] Among the compounds represented by the general formula (1), one which is represented by the general formula (11) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkyl group can also be synthesized by decarboxylation a compound obtained by performing a nucleophilic substitution on a lower alkyl dicarbonate corresponding to a compound of the general formula (4) with the leaving group attached.

[0034] In the general formulas (4) and (11),

R_1, R_2, R_3, R_4, R_6, R_7, R_8, X_1, X_2, X_3, X_4, m and n each have the same meanings as defined above; and
R_{14} is a lower alkyl group.

[0035] Stated more specifically, the compound represented by the general formula (11) can also be synthesized from the compound of the general formula (4) by desirably reacting it with a corresponding lower alkyl dicarbonate in the presence of a base such as sodium hydride in a solvent inert to the reaction as exemplified by dimethylformamide, tetra-

hydrofuran or acetonitrile, preferably in dimethylformamide, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature and thereafter subjecting the product to reaction in aqueous sulfuric acid at the boiling point of the reaction mixture.

[0036] Examples of the lower alkyl dicarbonate include dimethyl malonate, diethyl malonate, diethyl methylmalonate, diethyl ethylmalonate, diethyl n-propylmalonate, diethyl i-propylmalonate, diethyl n-butylmalonate, diethyl i-butylmalonate, diethyl t-butylmalonate, diethyl n-pentylmalonate and so forth.

[0037] Among the compounds represented by the general formula (1), one which is represented by the general formula (7) where A is an optionally substituted pyridine ring and one of the substituents present is an amino group can also be synthesized by reducing the nitro group in the corresponding general formula (6).

[0038] In the general formulas (6) and (7),

R_1, R_2, R_3, R_4, m and n each have the same meanings as defined above;
R_6, R_7, and R_8 are each a hydrogen atom, a halogen atom, a trifluoromethyl group, a hydroxyl group, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, NX_5X_6 or COX_7;
where X_5, X_6, and X_7 each have the same meanings as defined above;
X_1, X_2, X_3, and X_4 are each a hydrogen atom, a halogen atom, a phenyl group optionally substituted with a halogen atom and/or a lower alkyl group, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, NX_5X_6 or COX_7;
where X_5, X_6, and X_7, each have the same meanings as defined above.

[0039] Stated more specifically, the compound represented by the general formula (7) can also be synthesized by subjecting the compound of the general formula (6) to catalytic reduction in a solvent inert to the reaction as exemplified by ethanol, methanol, ethyl acetate, acetic acid or 1,4-dioxane, preferably in ethanol or methanol, in a hydrogen atmosphere at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature, with palladium-carbon, Raney nickel or platinum oxide used as a catalyst, or by performing reduction using nickel (II) chloride or sodium borohydride, so as to reduce the nitro group.

[0040] Among the compounds represented by the general formula (1), one which is represented by the general formula (8) where A is an optionally substituted pyridine ring and one of the substituents present is NR_9R_{10} can also be synthesized with a compound of the general formula (7) used as a starting material.

[0041] In the general formulas (7), (8), (15), (16) and (17),

R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_{12}, X_1, X_2, X_3, X_4, L, m and n each have the same meanings as defined above;
R_9 is a hydrogen atom or a lower alkyl group;
R_{10} is a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;
R_{13} is a lower alkyl group optionally substituted by a phenyl group; and
X is a halogen atom.

[0042] Stated more specifically, the compound represented by the general formula (8) can also be synthesized from the compound of the general formula (7) by desirably reacting it with a corresponding compound of the general formula (15), (16) or (17) in the presence of a base such as triethylamine or potassium carbonate in a solvent inert to the reaction at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature.

[0043] If in the process of synthesizing the compounds represented by the above formulas (1), (5), (7), (8) and (11), a protective group is necessary for the primary or secondary amino group, they are first protected either with a suitable resin or with one of the appropriate protective groups described in Green and Wuts, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS", 2nd Edition, John Wiley & Sons Inc., p. 309, 1991, and thereafter the respective reactions are performed. If necessary, the protected groups may be subjected to a deprotecting reaction. Examples of the amino protecting group include a t-butoxycarbonyl group, a trifluoroacetyl group and so forth.

[0044] The amino protecting reaction such as t-butoxycarbonylation may be performed by reacting the respective compound with di-t-butyl dicarbonate in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or methylene dichloride, dimethyl-formamide or 1,4-dioxane in the presence of an organic base such as triethylamine or 4-dimethylamiopyridine at a temperature between 0°C and room temperature.

[0045] The amino protecting reaction may also be performed with a Wang resin by reacting the respective compound with a 4-nitrophenyloxycarbonyl-Wang resin (Tetrahedron Lett., 37, 937-940 (1996)) in a solvent inert to the reaction as exemplified by methylene chloride, dimethylformamide or 1,4-dioxane in the presence of an organic base such as 4-methylmorpholine, triethylamine or 4-dimethylaminopyridine at a temperature between 0°C and room temperature.

[0046] If the protecting group is a t-butoxycarbonyl group or the Wang resin mentioned above, a reaction for deprotecting the amino group is preferably performed in a solvent inert to the reaction as exemplified by methanol, ethanol,

1,4-dioxane or methylene chloride or without using any solvent at all, with the aid of a deprotecting agent such as trifluoroacetic acid, hydrochloric acid, sulfuric acid or methanesulfonic acid at a temperature between 0°C and room temperature, with the use of anhydrous conditions, room temperature and trifluoroacetic acid being particularly preferred.

[0047] If the compounds of the invention which are represented by the general formula (1) have asymmetric carbons in their structure, the pure forms of their stereoisomers and optically active forms can be obtained by known techniques in the art, such as chromatography on optical isomer separating columns and fractional crystallization.

[0048] Pharmaceutically acceptable salts of the compounds of the invention which are represented by the general formula (1) may be of any types as long as they are pharmaceutically acceptable salts and typical examples include salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobrobromic acid and hydroiodic acid, salts with organic acids such as formic acid, acetic acid, oxalic acid and tartaric acid, salts with alkali metals such as sodium and potassium, and salts with alkaline earth metals such as calcium and magnesium.

[0049] The compounds of the invention or salts thereof may be formulated with suitable excipients, adjuvants, lubricants, antiseptics, disintegrators, buffering agents, binders, stabilizers, wetting agents, emulsifiers, coloring agents, flavoring agents, fragrances, etc. to form tablets, granules, subtilized granules, powders, capsules, syrups, elixirs, suspensions, emulsions, injections, etc. for oral or parenteral administration. When the cerebrovascular diseases to be treated are in a hyperacute phase (immediately after the stroke), an acute phase (from the stroke to 2 or 3 days later) or in a subacute phase (2 or 3 days up to 2 weeks after the stroke), administration is effected primarily by intramuscular or intravenous injection. In addition, oral administration may be performed in a chronic phase (the third week after stroke and onward) if the patient admits ingestion.

[0050] The compounds of the invention or salts thereof may be administered in doses that vary with the physical constitution of the patient, his or her age, physical condition, the severity of the disease, the time of lapse after the onset of the disease and other factors; typical daily doses range from 0.5 to 5 mg/body for oral administration and from 1 to 10 mg/body for parenteral administration. It should generally be noted that even if the same dose is administered, the plasma concentration may sometimes vary considerably between patients; hence, an optimal dose of the drug should ideally be determined for each patient on the basis of a monitored plasma concentration of the drug.

[0051] If the compounds of the invention or salts thereof are to be formulated as preparations for internal application, lactose, sucrose, sorbitol, mannitol, starches such as potato starch or corn starch, starch derivatives and common additives such as cellulose derivatives or gelatin are suitably used as vehicles, with lubricants such as magnesium stearate, carbowaxes and polyethylene glycol being optionally added concurrently; the resulting mixtures may be formulated in the usual manner into granules, tablets, capsules or other forms suitable for internal application.

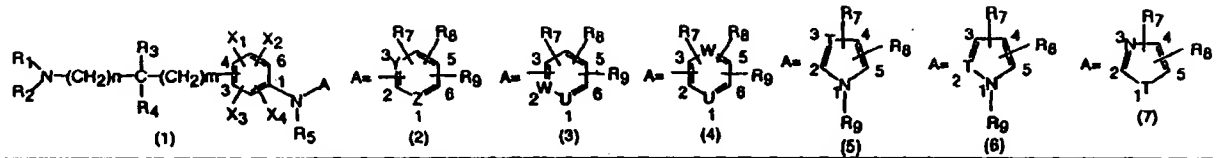
[0052] If the compounds of the invention or salts thereof are to be formulated as aqueous preparations, effective amounts of the principal ingredients may be dissolved in distilled water for injection, with antioxidants, stabilizers, dissolution aids, buffering agents, preservatives, etc. added as required and, after complete solutions are formed, they are filtered, filled into ampules and sealed in the usual manner and sterilized by a suitable medium such as high-pressure vapor or dry heat so as to prepare injections.

[0053] If the compounds of the invention or salts thereof are to be formulated as lyophilized preparations, aqueous solutions having the principal ingredients dissolved in distilled water for injection may be freeze-dried in the usual manner; depending on the need, excipients that provide for easy lyophilization, such as sugars (e.g. lactose, maltose and sucrose), sugar alcohols (e.g. mannitol and inositol), glycine and the like, may be added before freeze-drying is performed in the usual manner to make the intended preparations.

Examples

[0054] Lists of the compounds prepared in the Examples of the invention are given in Tables 1 - 37 below.

Table 1

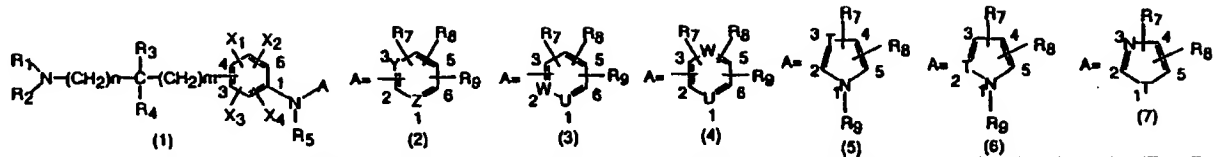


Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
1	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
2	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
3	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
4	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
5	(2)	CR_6	N	NHMe	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
6	(2)	CR_6	N	NHMe	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	
7	(2)	CR_6	N	NHEt	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
8	(2)	CR_6	N	NHEt	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
9	(2)	CR_6	N	H	2	4-H	5-NO_2	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
10	(2)	CR_6	N	H	2	4-H	5-NO_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
11	(2)	CR_6	N	H	2	4-H	5-NH_2	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
12	(2)	CR_6	N	H	2	4-H	5-NH_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
13	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
14	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
15	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	

*1:Numerals represent substitution positions in the structural formulas of (2)~(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★: W = $-(CH_2)_m-C(R_3)(R_4)-(CH_2)_n-N(R_1)(R_2)$

Table 2



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
16	(2)	CR_6	N	NH_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
17	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
18	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
19	(2)	CR_6	N	NH_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
20	(2)	CR_6	N	NH_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
21	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
22	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	HCl
23	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
24	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	H	H	0	H	H	0	H	HCl
25	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	$CO_2{}^tBu$	H	0	Indan-2-yl		0	H	
26	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	H	H	0	Indan-2-yl		0	H	HCl
27	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
28	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
29	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
30	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

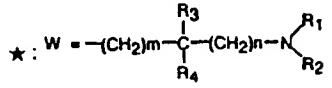
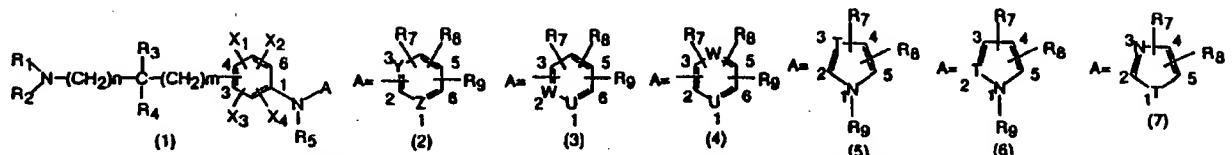


Table 3



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of R_9	R_1	R_2	n	R_3	R_4	m	R_5	salt
31	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHEt	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
32	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHEt	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
33	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NH^{n}Pr	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
34	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NH^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
35	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NMe_2	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
36	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NMe_2	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
37	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
38	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
39	(2)	CR_6	N	H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
40	(2)	CR_6	N	H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
41	(2)	CR_6	N	CF_3	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
42	(2)	CR_6	N	CF_3	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
43	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
44	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
45	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

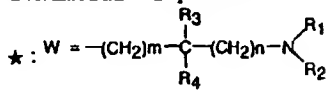
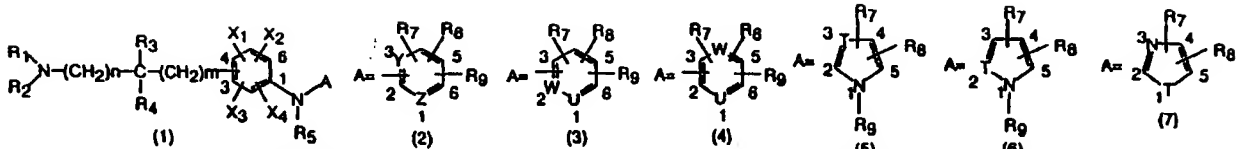


Table 4



Ex. No.	A	Y	Z.	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of R_9	R_1	R_2	n	R_3	R_4	m	R_5	salt
46	(2)	CR_6	N	H	2	4-OBn	5-H	6-H	2-H	4-H	5-H	6-H	3	Ac	H	0	H	H	0	H	HCl
47	(2)	CR_6	N	H	2	4-OBn	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
48	(2)	CR_6	N	H	2	4-H	5-H	6-H	2-H	4-cyclobutyl	5-H	6-H	3	Bz	H	0	H	H	0	H	HCl
49	(2)	CR_6	N	H	2	4-H	5-H	6-H	2-H	4-cyclopentyl	5-H	6-H	3	H	H	0	H	H	0	H	HCl
50	(2)	CR_6	N	H	2	4-H	5-H	6-H	2-H	4-piperidino	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
51	(2)	CR_6	N	H	2	4-H	5-H	6-H	2-H	4-$O(CH_2)_2Ph$	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
52	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
53	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
54	(2)	CR_6	N	NO_2	2	4-H	5-H	6-^{n}Pr	2-H	4-H	5-H	6-H	3	Bn	H	0	H	H	0	H	HCl
55	(2)	CR_6	N	NO_2	2	4-H	5-H	6-^{i}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
56	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OH	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
57	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OEt	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
58	(2)	CR_6	N	NO_2	2	4-H	5-H	6-O^nPr	2-H	4-H	5-H	6-H	3	CH_2CH_2Ph	H	0	H	H	0	H	HCl
59	(2)	CR_6	N	NO_2	2	4-H	5-H	6-O^iPr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
60	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SH	2-H	4-H	5-H	6-H	3	CH_2CH_2Cl	CH_2CH_2Cl	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

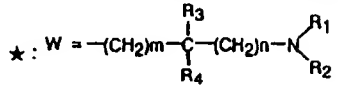
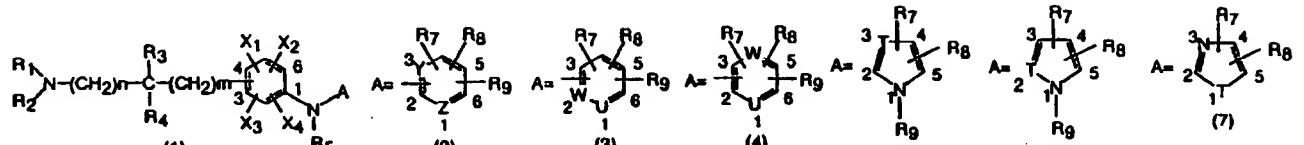


Table 5



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
61	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
62	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SEt	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
63	(2)	CR_6	N	NO_2	2	4-H	5-H	6-S^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Me	HCl
64	(2)	CR_6	N	NO_2	2	4-H	5-H	6-S^{i}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Et	HCl
65	(2)	CR_6	N	H	2	4-NO_2	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
66	(2)	CR_6	N	H	2	4-NO_2	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
67	(2)	CR_6	N	H	2	4-H	5-NO_2	6-OMe	2-H	4-H	5-NHAc	6-H	3	H	H	0	H	H	0	H	HCl
68	(2)	CR_6	N	H	2	4-H	5-NO_2	6-Et	2-H	4-NHBn	5-H	6-H	3	H	H	0	H	H	0	H	HCl
69	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-OMe	2-H	4-NO_2	5-H	6-H	3	H	H	0	H	H	0	^{n}Pr	HCl
70	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-Et	2-H	4-H	5-NO_2	6-H	3	H	H	0	H	H	0	Ac	HCl
71	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Bn	HCl
72	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
73	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-OMe	2-H	4-F	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
74	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-Et	2-H	4-H	5-Br	6-H	3	H	H	0	H	H	0	H	2HCl
75	(2)	CR_6	N	CF_3	2	4-H	5-H	6-OMe	2-H	4-CH_2Br	5-H	6-H	3	H	H	0	H	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

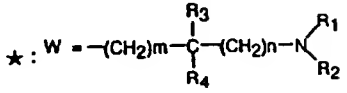
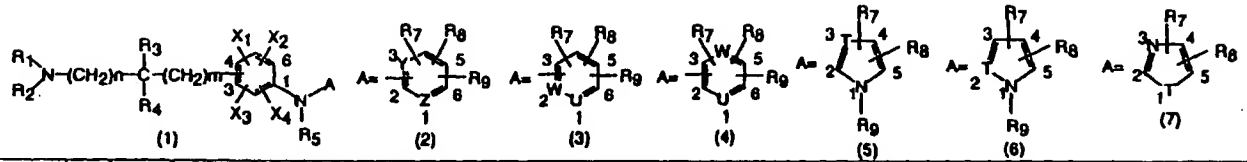


Table 6



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
76	(2)	CR_6	N	CF_3	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
77	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	HCl
78	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-^{n}Pr	5-H	6-H	3	H	H	0	H	H	0	H	HCl
79	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-NHMe	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
80	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-NHEt	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
81	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-NMe_2	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
82	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-pyrrolidin-1-yl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
83	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-OH	5-H	6-H	3	H	H	0	H	H	0	H	HCl
84	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-OEt	5-H	6-H	3	H	H	0	H	H	0	H	HCl
85	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-Me	6-H	3	H	H	0	H	H	0	H	HCl
86	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-F	4-H	5-Et	6-H	3	H	H	0	CH_2CH_2OH	CH_2CH_2OH	0	H	HCl
87	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-Cl	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
88	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-Me	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
89	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-OH	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
90	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-OMe	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

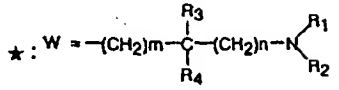
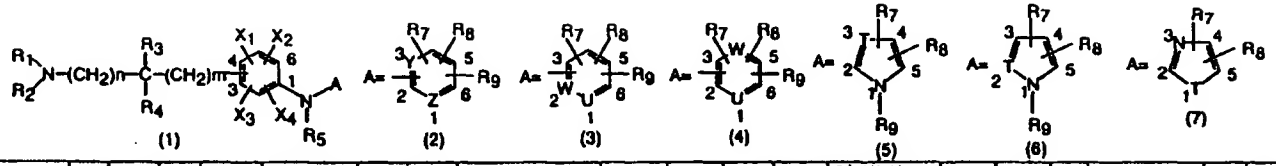


Table 7



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
91	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
92	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-CN	5-H	6-H	3	H	H	0	Et	H	0	H	HCl
93	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-CN	5-H	6-H	3	H	H	0	^nPr	H	0	H	HCl
94	(2)	CR_6	N	NO_2	2	4-H	5-H	6-cyclobutylthio	2-H	4-H	5-H	6-H	3	H	H	0	Me	Me	0	H	HCl
95	(2)	CR_6	N	NO_2	2	4-H	5-H	6-cyclopentylthio	2-H	4-H	5-H	6-H	3	H	H	0	$-(CH_2)_2-$		0	H	HCl
96	(2)	CR_6	N	NO_2	2	4-H	5-H	6-cyclohexylthio	2-H	4-H	5-H	6-H	3	H	H	0	$-(CH_2)_3-$		0	H	HCl
97	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	$-(CH_2)_4-$		0	H	HCl
98	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	Me	H	0	H	H	0	H	HCl
99	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	Et	H	0	H	H	0	H	HCl
100	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OMe	4-H	5-H	6-H	3	Me	Me	0	H	H	0	H	HCl
101	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OMe	4-H	5-H	6-H	3	$-(CH_2)_3-$		0	H	H	0	H	HCl
102	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$-(CH_2)_4-$		0	H	H	0	H	HCl
103	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$-(CH_2)_6-$		0	H	H	0	H	HCl
104	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	CH_2OH	H	0	H	HCl
105	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	CH_2CH_2OH	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

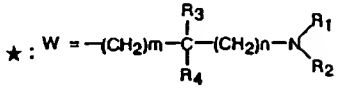
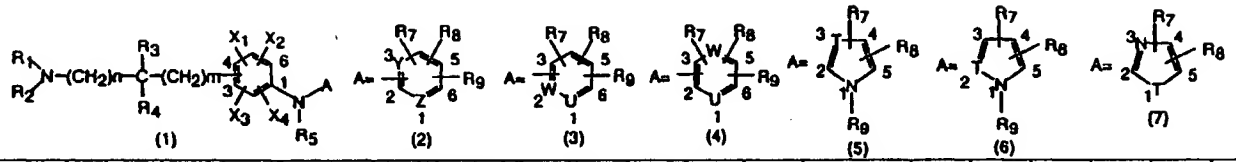


Table 8



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
106	(2)	CR_6	N	H	2	4-OMe	5-H	6-NO_2	2-H	4-Ph	5-H	6-H	3	H	H	0	H	H	0	H	HCl
107	(2)	CR_6	N	OH	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
108	(2)	CR_6	N	CHO	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
109	(2)	CR_6	N	CO_2H	4	2-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
110	(2)	CR_6	N	$CONH_2$	4	2-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
111	(2)	CR_6	N	CO_2Me	4	2-H	5-H	6-OMe	2-H	4-H	5-Me	6-Me	3	H	H	0	H	H	0	H	HCl
112	(2)	CR_6	N	CN	4	2-H	5-H	6-Et	2-Me	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	HCl
113	(2)	CR_6	N	CF_3	5	2-Me	4-H	6-H	2-H	4-H	5-Br	6-H	3	H	H	0	H	H	0	H	2HCl
114	(2)	CR_6	N	NO_2	4	2-H	5-OEt	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
115	(2)	CR_6	N	H	5	2-H	4-NO_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
116	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Me	HCl
117	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Et	HCl
118	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	^nPr	HCl
119	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OEt	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Ac	HCl
120	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	Bz	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

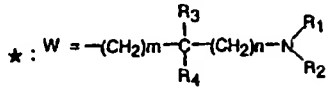
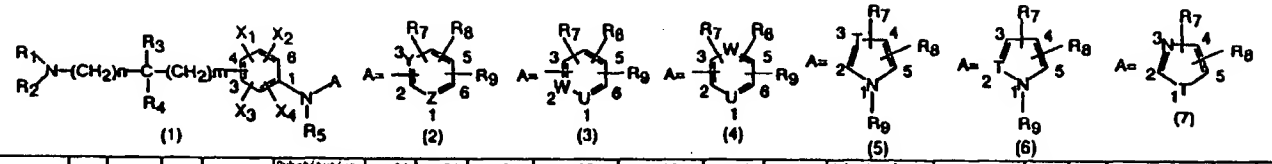


Table 9



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
121	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SMe	2-H	4-H	5-H	6-H	2	H	H	0	H	H	0	CO_2Me	HCl
122	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SEt	2-H	4-H	5-H	6-H	2	H	H	0	H	H	0	CO_2Et	HCl
123	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-Ph	6-H	2	H	H	0	Me	Me	0	H	HCl
124	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-$CONH_2$	5-H	6-H	2	H	H	0	CH_2OH	H	0	H	HCl
125	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-Me	4-H	5-H	6-H	2	H	H	0	CH_2Br	H	0	H	HCl
126	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-Me	4-H	5-H	6-H	2	H	H	0	H	H	0	H	HCl
127	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-CH_2OH	4-H	5-H	6-H	2	H	H	0	H	H	0	H	HCl
128	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	2	H	H	0	Bn	H	0	H	HCl
129	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-Me	2-Me	4-H	5-H	6-H	2	H	H	0	CH_2CH_2Ph	H	0	H	HCl
130	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	2	H	H	0	CH_2OH	H	0	H	HCl
131	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-NO_2	2	H	H	0	H	H	0	H	HCl
132	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-Me	2-Cl	4-OMe	5-H	6-H	2	H	H	0	H	H	0	H	HCl
133	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-OMe	2-H	4-NHAc	5-H	6-H	2	H	H	0	H	H	0	H	HCl
134	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-Et	2-Me	4-H	5-H	6-H	2	H	H	0	H	H	0	H	HCl
135	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-Et	2-H	4-$CONH_2$	5-H	6-H	2	CH_2CH_2F	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

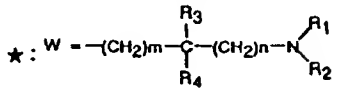
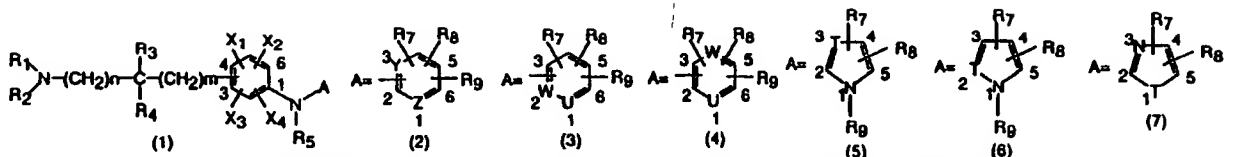


Table 10



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
136	(2)	CR_6	N	H	4	2-$CONMe_2$	5-H	6-OMe	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
137	(2)	CR_6	N	H	4	2-CONHMe	5-H	6-Et	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
138	(2)	CR_6	N	H	4	2-NHAc	5-H	6-H	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
139	(2)	CR_6	N	H	4	2-$NHCO_2Me$	5-H	6-H	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
140	(2)	CR_6	N	H	4	2-NHBz	5-H	6-H	2-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
141	(2)	CR_6	N	NO_2	5	2-H	4-H	6-F	2-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	HCl
142	(2)	CR_6	N	NO_2	5	2-H	4-H	6-Br	2-H	3-H	5-H	6-H	4	H	H	0	H	H	1	H	HCl
143	(2)	CR_6	N	NO_2	5	2-H	4-H	6-H	2-CO_2H	3-H	5-H	6-H	4	H	H	0	H	H	1	H	HCl
144	(2)	CR_6	N	NO_2	5	2-H	4-H	6-H	2-H	3-CO_2Me	5-H	6-H	4	H	H	0	H	H	1	H	HCl
145	(2)	CR_6	N	NO_2	5	2-H	4-H	6-H	2-H	3-CONHMe	5-H	6-H	4	H	H	0	H	H	1	H	HCl
146	(2)	CR_6	N	NO_2	5	2-H	4-H	6-H	2-H	3-H	5-CHO	6-H	4	H	H	0	H	H	1	H	HCl
147	(2)	CR_6	N	H	2	3-H	4-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	CHO	HCl
148	(2)	CR_6	N→O	H	2	3-H	4-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
149	(2)	CR_6	N→O	H	2	3-H	4-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
150	(2)	CR_6	N→O	H	2	3-H	4-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

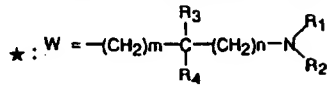
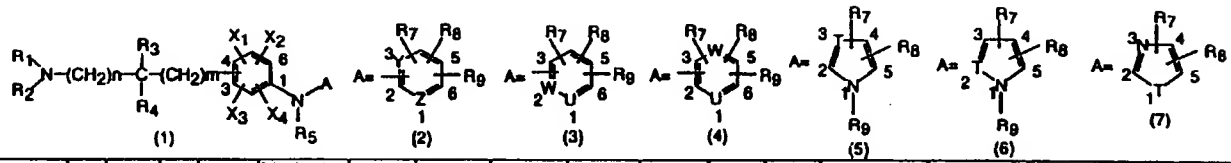


Table 11



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
151	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
152	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
153	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
154	(2)	CR_6	CH	NO_2	2	4-H	5-NHMe	6-H	2-H	4-H	5-H	6-H	3	CH_2CH_2F	CH_2CH_2F	0	H	H	0	H	2HCl
155	(2)	CR_6	CH	NO_2	2	4-H	5-NMe_2	6-H	2-H	4-H	5-H	6-H	3	CH_2CH_2Cl	CH_2CH_2Cl	0	H	H	0	H	2HCl
156	(2)	CR_6	CH	NO_2	2	4-H	5-NHEt	6-H	2-H	4-H	5-H	6-H	3	CH_2CH_2Br	CH_2CH_2Br	0	H	H	0	H	2HCl
157	(2)	CR_6	CH	NO_2	2	4-SMe	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
158	(2)	CR_6	CH	NO_2	2	4-SEt	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
159	(2)	CR_6	CH	NO_2	2	4-S^{n}Pr	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
160	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-Me	2-Me	4-H	5-H	6-H	3	H	H	0	$-(CH_2)_2-$		0	H	HCl
161	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-^{n}Pr	2-H	4-Et	5-H	6-H	3	H	H	0	$-(CH_2)_3-$		0	H	HCl
162	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-NH^{n}Pr	2-H	4-H	5-^{n}Pr	6-H	3	H	H	0	$-(CH_2)_4-$		0	H	2HCl
163	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-F	2-NHBn	4-H	5-H	6-H	3	$-(CH_2)_2-$		0	H	H	0	H	2HCl
164	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-Cl	2-H	4-NHEt	5-H	6-H	3	$-(CH_2)_3-$		0	H	H	0	H	2HCl
165	(2)	CR_6	CH	CO_2H	2	4-H	5-H	6-Br	2-H	4-H	5-H	6-SEt	3	$-(CH_2)_4-$		0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

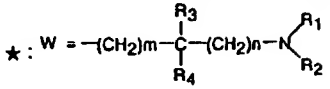
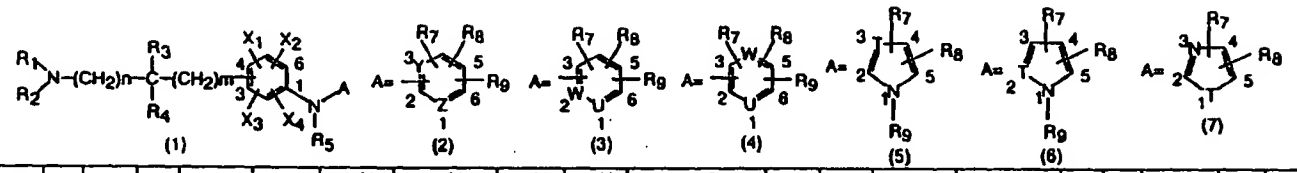


Table 12



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
166	(2)	CR_6	CH	CO_2Me	2	4-H	5-H	6-Me	2-H	4-pyrrolidin-1-yl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
167	(2)	CR_6	CH	CO_2Me	2	4-H	5-H	6-Et	2-H	4-pyrrolidin-1-yl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
168	(2)	CR_6	CH	CO_2Me	2	4-H	5-H	6-OMe	2-OMe	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
169	(2)	CR_6	CH	H	2	4-H	5-$CONH_2$	6-Me	2-OEt	4-H	5-H	6-H	3	Bn	H	0	H	H	0	H	HCl
170	(2)	CR_6	CH	H	2	4-H	5-$CONH_2$	6-Me	2-H	4-OBn	5-H	6-H	3	CH_2CH_2Ph	H	0	H	H	0	H	HCl
171	(2)	CR_6	CH	H	2	4-H	5-$CONMe_2$	6-Me	2-F	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
172	(2)	CR_6	CH	H	2	4-H	5-$CONMe_2$	6-Me	2-Cl	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
173	(2)	CR_6	CH	H	2	4-NHAc	5-H	6-Me	2-Br	4-H	5-H	6-H	3	Ac	H	0	H	H	0	H	
174	(2)	CR_6	CH	H	2	4-NHAc	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
175	(2)	CR_6	CH	H	2	4-NHAc	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
176	(2)	CR_6	CH	H	2	4-NHBn	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
177	(2)	CR_6	CH	H	2	4-NHBn	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	Me	Me	0	H	HCl
178	(2)	CR_6	CH	H	2	4-NHBz	5-H	6-Me	2-H	4-H	5-H	6-H	3	Bz	H	0	Me	Et	0	H	
179	(2)	CR_6	CH	CF_3	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	Bn	H	0	H	HCl
180	(2)	CR_6	CH	CF_3	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	CH_2OH	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

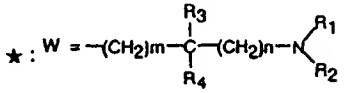
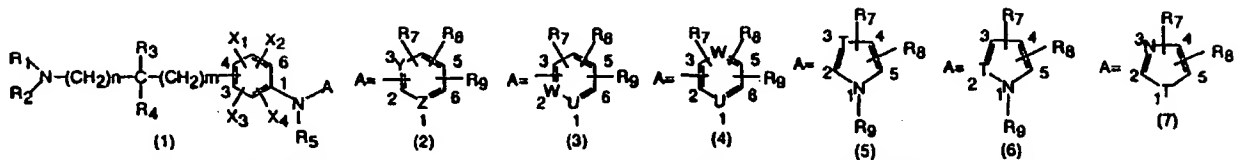
★: 

Table 13

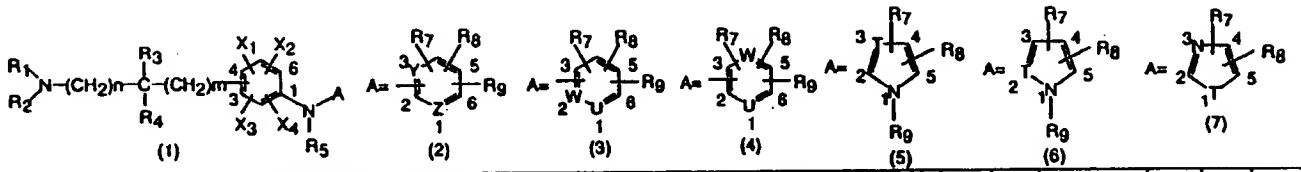


Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
181	(2)	CR_6	CH	CN	2	4-H	5-H	6-cyclobutyl	2-H	4-OH	5-H	6-H	3	H	H	0	H	H	0	H	HCl
182	(2)	CR_6	CH	CN	2	4-H	5-H	6-cyclopentyl	2-H	4-H	5-CN	6-H	3	H	H	0	H	H	0	H	HCl
183	(2)	CR_6	CH	CN	2	4-H	5-H	6-cyclohexyl	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
184	(2)	CR_6	CH	OH	2	4-H	5-H	6-H	2-H	4-H	5-H	6-NO_2	3	H	H	0	CH_2CH_2OH	CH_2CH_2OH	0	H	2HCl
185	(2)	CR_6	CH	OH	2	4-H	5-H	6-H	2-H	4-H	5-H	6-OH	3	H	H	0	H	H	0	H	2HCl
186	(2)	CR_6	CH	NH_2	2	4-H	5-NHCOMe	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
187	(2)	CR_6	CH	NH_2	2	4-H	5-$NHCO_2Me$	6-H	2-H	4-CH_2Ph	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
188	(2)	CR_6	CH	NH_2	2	4-H	5-CHO	6-H	2-H	4-CH_2OH	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
189	(2)	CR_6	CH	NH_2	2	4-H	5-H	6-H	2-CH_2OH	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
190	(2)	CR_6	CMe	CHO	2	4-H	5-H	6-cyclobutylthio	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
191	(2)	CR_6	CH	CHO	2	4-H	5-H	6-cyclopentylthio	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
192	(2)	CR_6	CH	CHO	2	4-H	5-H	6-cyclohexylthio	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
193	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-H	2-OH	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
194	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-H	2-CN	4-H	5-H	6-H	3	Me	H	0	H	H	0	H	HCl
195	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-NO_2	3	Me	Me	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★: W = $-(CH_2)_m-C(R_3)(R_4)-(CH_2)_n-N(R_1)(R_2)$

Table 14



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
196	(2)	CR_6	CH	H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-NO_2	3	H	Me	0	Me	H	0	H	HCl
197	(2)	CR_6	CH	H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-NO_2	3	Me	Me	0	H	H	0	H	HCl
198	(2)	CR_6	CEt	H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	HCl
199	(2)	CR_6	CH	H	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	HCl
200	(2)	CR_6	CH	H	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	Ac	HCl
201	(2)	CR_6	CH	H	2	4-H	5-H	6-Et	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	Me	HCl
202	(2)	CR_6	CH	H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	Ac	HCl
203	(2)	CR_6	CH	H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	^{n}Pr	HCl
204	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Me	2-H	3-H	5-H	6-H	4	H	H	0	H	H	1	CO_2Me	HCl
205	(2)	CR_6	C^{n}Pr	NO_2	2	4-H	5-H	6-Me	2-H	3-H	5-H	6-H	4	H	H	0	H	H	1	CO_2Et	HCl
206	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Me	2-H	3-H	5-H	6-H	4	H	H	0	CH_2OH	H	1	H	HCl
207	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Me	2-H	3-H	5-H	6-H	4	H	H	0	CH_2Ph	H	1	H	HCl
208	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	3-H	4-H	6-H	5	H	H	1	H	H	0	H	HCl
209	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	3-H	4-H	6-H	5	H	H	1	CH_2CH_2Ph	H	0	H	HCl
210	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	3-H	4-H	6-H	5	H	H	1	CH_2Ph	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

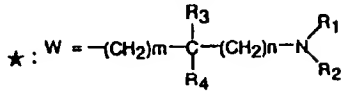
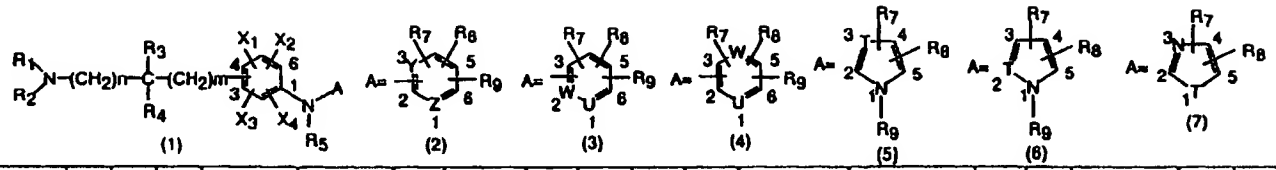


Table 15



Ex. No.	A	Y	Z	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
211	(2)	N	N	2	4-NO_2	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
212	(2)	N	N	2	4-NO_2	5-H	6-Et	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
213	(2)	N	N	2	4-NO_2	5-H	6-^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
214	(2)	N	N	2	4-NO_2	5-H	6-^{i}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
215	(2)	N	N	2	4-CO_2H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
216	(2)	N	N	2	4-CO_2H	5-H	6-OEt	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
217	(2)	N	N	2	4-CO_2H	5-H	6-O^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
218	(2)	N	N	2	4-CO_2H	5-H	6-O^{i}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
219	(2)	N	N	2	4-CO_2Me	5-H	6-NHMe	2-H	4-H	5-H	6-H	3	Bn	H	0	H	H	0	H	HCl
220	(2)	N	N	2	4-CO_2Me	5-H	6-NMe_2	2-H	4-H	5-H	6-H	3	CH_2CH_2Ph	H	0	H	H	0	H	HCl
221	(2)	N	N	2	4-CO_2Et	5-H	6-NHEt	2-H	4-H	5-H	6-H	3	$CH_2(CH_2)_2Ph$	H	0	H	H	0	H	HCl
222	(2)	N	N	2	4-CO_2Et	5-H	6-NH^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
223	(2)	N	N	2	4-CO_2Et	5-H	6-H	2-Me	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
224	(2)	N	N	2	4-$CO_2{}^n$Pr	5-H	6-H	2-Et	4-H	5-H	6-H	3	H	H	0	Bn	H	0	H	HCl
225	(2)	N	N	2	4-$CO_2{}^n$Pr	5-H	6-H	2-^{n}Pr	4-H	5-H	6-H	3	H	H	0	CH_2CH_2Ph	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

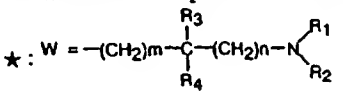
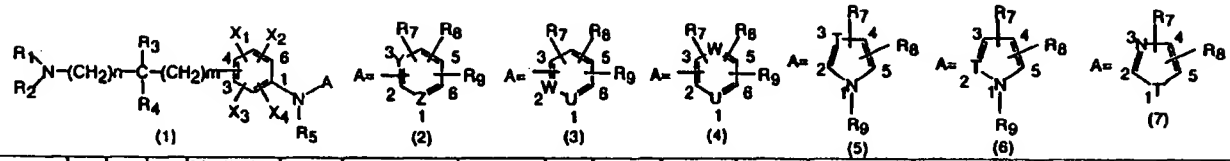
★: 

Table 16



Ex. No.	A	Y	Z	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
226	(2)	N	N	4	2-CF_3	5-H	6-H	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
227	(2)	N	N	4	2-CF_3	5-H	6-H	2-H	4-OEt	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
228	(2)	N	N	4	2-CF_3	5-H	6-H	2-H	4-O^{n}Pr	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
229	(2)	N	N	4	2-H	5-CN	6-H	2-H	3-H	5-NHMe	6-H	4	Ac	H	1	H	H	0	H	HCl
230	(2)	N	N	4	2-H	5-CN	6-H	2-H	3-H	5-NHEt	6-H	4	Bz	H	1	H	H	0	H	HCl
231	(2)	N	N	4	2-H	5-CN	6-H	2-H	3-H	5-NH^{n}Pr	6-H	4	$CO_2{}^t$Bu	H	1	H	H	0	H	
232	(2)	N	N	4	2-H	5-H	6-$CONH_2$	2-H	3-H	5-H	6-SMe	4	H	H	1	H	H	0	H	2HCl
233	(2)	N	N	4	2-H	5-H	6-$CONH_2$	2-H	3-H	5-H	6-SEt	4	H	H	1	H	H	0	H	2HCl
234	(2)	N	N	4	2-H	5-H	6-$CONH_2$	2-H	3-H	5-H	6-S^{n}Pr	4	H	H	1	H	H	0	H	2HCl
235	(2)	N	N	5	2-OMe	4-H	6-H	3-H	4-H	5-H	6-NO_2	2	Me	H	1	H	H	0	H	2HCl
236	(2)	N	N	5	2-OEt	4-H	6-H	3-H	4-H	5-H	6-NO_2	2	Me	Me	1	H	H	0	H	2HCl
237	(2)	N	N	5	2-H	4-cyclopropyl	6-H	3-H	4-H	5-H	6-NO_2	2	Et	H	1	H	H	0	H	2HCl
238	(2)	N	N	5	2-H	4-cyclobutyl	6-H	3-H	4-H	5-H	6-NO_2	2	Et	Et	1	H	H	0	H	2HCl
239	(2)	N	N	5	2-H	4-cyclopentyl	6-H	3-H	4-H	5-H	6-CO_2H	2	CH_2CH_2Cl	CH_2CH_2Cl	1	H	H	0	H	2HCl
240	(2)	N	N	5	2-H	4-cyclohexyl	6-H	3-H	4-H	5-H	6-CO_2H	2	CH_2CH_2Br	CH_2CH_2Br	1	H	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

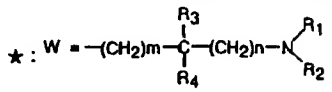
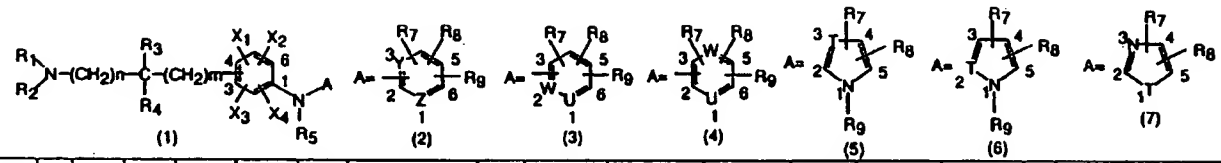


Table 17



Ex. No.	A	Y	Z	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
241	(2)	N	N	2	4-CHO	5-H	6-H	2-H	4-NHAc	5-H	6-H	3	$-CH_2CH_2-$		0	H	H	0	H	HCl
242	(2)	N	N	2	4-CHO	5-H	6-H	2-H	4-NHBz	5-H	6-H	3	$-CH_2CH_2CH_2-$		0	H	H	0	H	HCl
243	(2)	N	N	2	4-NH_2	5-H	6-H	2-H	4-H	5-$CONH_2$	6-H	3	$-CH_2(CH_2)_2CH_2-$		0	H	H	0	H	2HCl
244	(2)	N	N	2	4-NH_2	5-H	6-H	2-H	4-H	5-CONHMe	6-H	3	H	H	0	Me	H	0	Me	2HCl
245	(2)	N	N	2	4-NH_2	5-H	6-H	2-H	4-H	5-CONHEt	6-H	3	H	H	0	Me	Me	0	Et	2HCl
246	(2)	N	N	2	4-H	5-OH	6-H	2-H	4-H	5-H	6-CO_2Me	3	H	H	0	Et	H	0	^{n}Pr	2HCl
247	(2)	N	N	2	4-H	5-OH	6-H	2-H	4-H	5-H	6-CO_2Et	3	H	H	0	Et	Et	0	CHO	HCl
248	(2)	N	N	2	4-H	5-H	6-pyrrolidin-1-yl	2-H	4-H	5-H	6-$CO_2{}^n$Pr	3	H	H	0	$-CH_2CH_2-$		0	Ac	2HCl
249	(2)	N	N	2	4-H	5-H	6-piperidino	2-H	4-CH_2OH	5-H	6-H	3	H	H	0	$-CH_2CH_2CH_2-$		0	Bz	2HCl
250	(2)	N	N	2	4-H	5-H	6-H	2-H	4-F	5-H	6-H	3	H	H	0	$-CH_2(CH_2)_2CH_2-$		0	CO_2Et	HCl
251	(2)	N	N	2	4-H	5-H	6-H	2-H	4-Cl	5-H	6-H	3	H	H	0	H	H	0	$CO_2{}^n$Pr	HCl
252	(2)	N	N	2	4-H	5-H	6-H	2-H	4-Br	5-H	6-H	3	H	H	0	H	H	0	$CO_2{}^t$Bu	HCl
253	(2)	N→O	N→O	2	4-H	5-H	6-H	2-H	4-H	5-CH_2Br	6-H	3	H	H	0	CH_2CH_2F	CH_2CH_2F	0	H	HCl
254	(2)	N→O	N→O	2	4-H	5-H	6-H	2-H	4-H	5-CN	6-H	3	H	H	0	CH_2CH_2Cl	CH_2CH_2Cl	0	H	HCl
255	(2)	N→O	N→O	2	4-H	5-H	6-H	2-H	4-H	5-CF_3	6-H	3	H	H	0	CH_2CH_2Br	CH_2CH_2Br	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

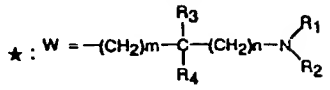
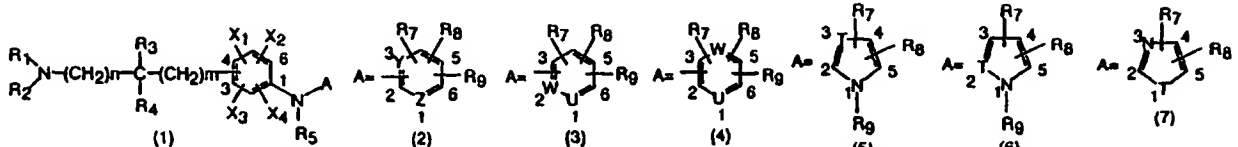


Table 18



(1) (2) (3) (4) (5) (6) (7)

Ex. No.	A	T	R_6	Substitution position of A	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
256	(5)	CR_6	NO_2	2	4-H	5-Me	H	2-H	4-OMe	5-H	6-H	3	Me	H	0	H	H	0	Me	HCl
257	(5)	CR_6	NO_2	2	4-H	5-Et	H	2-H	4-OEt	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
258	(5)	CR_6	NO_2	2	4-H	5-^{n}Pr	Me	2-H	4-O^{n}Pr	5-H	6-H	3	H	H	0	H	H	0	Et	HCl
259	(5)	CR_6	NO_2	2	4-H	5-^{i}Pr	H	2-H	4-O^{i}Pr	5-H	6-H	3	H	H	0	H	H	0	H	HCl
260	(5)	CR_6	CO_2H	2	4-H	5-OMe	H	2-Me	4-H	5-H	6-H	3	Et	H	0	H	H	0	H	HCl
261	(5)	CR_6	CO_2H	2	4-H	5-OEt	H	2-Et	4-H	5-H	6-H	3	H	H	0	Et	H	0	^{n}Pr	HCl
262	(5)	CR_6	CO_2H	2	4-H	5-O^{n}Pr	Et	2-^{n}Pr	4-H	5-H	6-H	3	H	H	0	H	H	0	^{i}Pr	HCl
263	(5)	CR_6	CO_2Me	2	4-H	5-SMe	H	2-H	4-H	5-NO_2	6-H	3	^{n}Pr	H	0	H	H	0	H	HCl
264	(5)	CR_6	CO_2Et	2	4-H	5-SEt	H	2-H	4-H	5-NO_2	6-H	3	H	H	0	^{n}Pr	H	0	H	HCl
265	(5)	CR_6	$CO_2{}^n$Pr	2	4-H	5-S^{n}Pr	^{n}Pr	2-H	4-H	5-NO_2	6-H	3	H	H	0	H	H	0	Ac	HCl
266	(5)	CR_6	CN	2	4-H	5-H	H	2-H	4-H	5-H	6-CO_2H	3	$-CH_2CH_2-$		0	H	H	0	H	HCl
267	(5)	CR_6	CN	2	4-H	5-H	H	2-H	4-H	5-H	6-CO_2Me	3	H	H	0	$-CH_2CH_2-$		0	H	HCl
268	(5)	CR_6	CN	2	4-H	5-H	H	2-H	4-H	5-H	6-CO_2Et	3	H	H	0	H	H	0	Bz	HCl
269	(5)	CR_6	CF_3	2	4-H	5-H	H	2-H	4-NH_2	5-H	6-H	3	CH_2CH_2F	H	0	H	H	0	H	2HCl
270	(5)	CR_6	CF_3	2	4-H	5-H	H	2-H	4-$CONH_2$	5-H	6-H	3	H	H	0	CH_2CH_2F	H	0	CHO	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

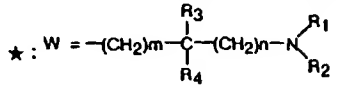
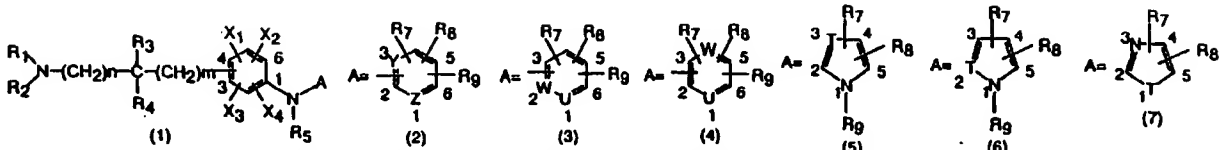


Table 19



(1) (2) (3) (4) (5) (6) (7)

Ex. No.	A	T	R_6	Substitution position of R_6	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of R_9	R_1	R_2	n	R_3	R_4	m	R_5	salt
271	(5)	CR_6	H	4	2-CHO	5-H	H	2-F	3-H	5-H	6-H	4	H	H	1	H	H	0	CO_2Me	HCl
272	(5)	CR_6	H	4	2-CHO	5-H	H	2-Cl	3-H	5-H	6-H	4	H	H	1	H	H	0	CO_2Et	HCl
273	(5)	CR_6	H	4	2-H	5-NHAc	Ac	2-Br	3-H	5-H	6-H	4	Ac	H	1	H	H	0	H	
274	(5)	CR_6	H	4	2-H	5-NHBz	H	2-H	3-H	5-H	6-H	4	Bz	H	1	H	H	0	H	
275	(5)	CR_6	H	4	2-$CONH_2$	5-H	H	2-H	3-H	5-H	6-H	4	Me	Me	1	H	H	0	H	2HCl
276	(5)	CR_6	H	4	2-CONHMe	5-H	Bz	2-H	3-H	5-H	6-H	4	H	H	1	Me	Me	0	H	2HCl
277	(5)	CR_6	H	4	2-H	5-CONHEt	H	2-H	3-H	4-H	5-H	6	CO_2Et	H	0	H	H	1	H	
278	(5)	CR_6	H	4	2-H	5-CONH^{n}Pr	H	2-H	3-H	4-H	5-H	6	H	H	0	H	H	1	H	2HCl
279	(5)	CR_6	H	4	2-F	5-H	CO_2Me	2-H	3-NHAc	4-H	5-H	6	$CO_2{}^t$Bu	H	0	H	H	1	H	
280	(5)	CR_6	H	4	2-Cl	5-H	H	2-H	3-NHBz	4-H	5-H	6	H	H	0	H	H	1	H	2HCl
281	(5)	CR_6	H	4	2-Br	5-H	H	2-H	2-CONHMe	4-H	5-H	6	H	H	0	H	H	1	H	2HCl
282	(5)	CR_6	NHMe	4	2-H	5-H	CO_2Et	2-H	3-H	4-H	5-H	6	CH_2CH_2Cl	CH_2CH_2Cl	0	H	H	1	H	HCl
283	(5)	CR_6	NHEt	4	2-H	5-H	H	2-H	3-H	4-H	5-H	6	H	H	0	CH_2CH_2Br	CH_2CH_2Br	1	H	2HCl
284	(5)	CR_6	NH^{n}Pr	4	2-H	5-H	H	2-H	3-H	4-H	5-H	6	H	H	0	H	H	1	H	2HCl
285	(5)	CR_6	H	4	2-OH	5-H	$CO_2{}^t$Bu	2-H	3-H	4-H	5-H	6	H	H	0	H	H	1	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

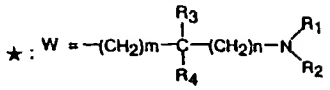
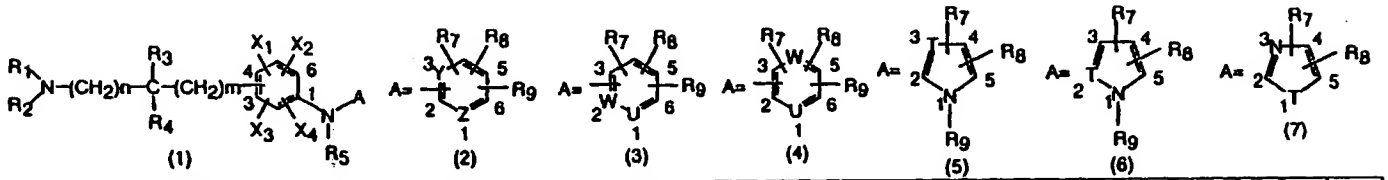
★: W = 

Table 20

【表20】

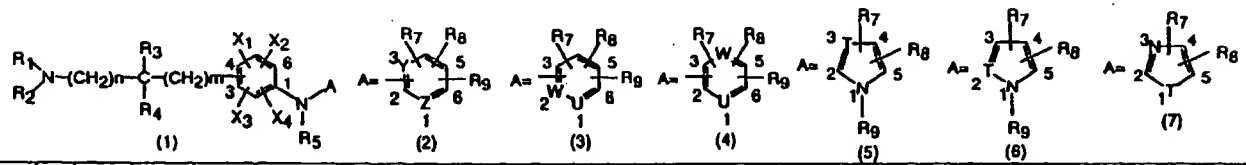


Ex. No.	A	T	Substitution position of A	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
286	(5)	N	2	4-NO_2	5-H	Me	2-Me	4-H	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
287	(5)	N	2	4-NO_2	5-H	H	2-Et	4-H	5-H	6-H	3	Me	H	0	H	H	0	Me	HCl
288	(5)	N	2	4-CO_2H	5-H	H	2-H	4-^{n}Pr	5-H	6-H	3	H	H	0	Et	H	0	H	HCl
289	(5)	N	2	4-CO_2H	5-H	Et	2-H	4-^{i}Pr	5-H	6-H	3	Et	H	0	H	H	0	Et	HCl
290	(5)	N	2	4-CF_3	5-H	H	2-H	4-H	5-OMe	6-H	3	H	H	0	^{n}Pr	H	0	H	2HCl
291	(5)	N	2	4-CF_3	5-H	H	2-H	4-H	5-OEt	6-H	3	^{n}Pr	H	0	H	H	0	Ac	HCl
292	(5)	N	2	4-CO_2Me	5-H	^{n}Pr	2-H	4-H	5-H	6-NHMe	3	H	H	0	H	H	0	H	2HCl
293	(5)	N	2	4-CO_2Me	5-H	H	2-H	4-H	5-H	6-NHEt	3	$-CH_2CH_2-$		0	H	H	0	Bz	HCl
294	(5)	N	2	4-CO_2Et	5-H	H	2-SMe	4-H	5-H	6-H	3	H	H	0	$-CH_2CH_2-$		0	H	HCl
295	(5)	N	2	4-CO_2Et	5-H	^{i}Pr	2-SEt	4-H	5-H	6-H	3	Ac	H	0	H	H	0	H	
296	(5)	N	2	4-CN	5-H	H	2-H	4-OH	5-H	6-H	3	H	H	0	CH_2CH_2F	H	0	H	HCl
297	(5)	N	2	4-CN	5-H	H	2-H	4-F	5-H	6-H	3	Bz	H	0	H	H	0	H	
298	(5)	N	2	4-NH_2	5-H	Ac	2-H	4-H	5-Cl	6-H	3	H	H	0	H	H	0	H	2HCl
299	(5)	N	2	4-NHAc	5-H	H	2-H	4-H	5-Br	6-H	3	$CO_2{}^t$Bu	H	0	H	H	0	H	
300	(5)	N	2	4-NHMe	5-H	H	2-H	4-H	5-H	6-H	3	H	H	0	CH_2CH_2Cl	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★: W = $-(CH_2)m-C(R_3)(R_4)-(CH_2)n-N(R_1)(R_2)$

Table 21



Ex. No.	A	T	Substitution position of A	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
301	(5)	N	2	4-H	5-NMe_2	Bz	2-H	4-H	5-H	6-NO_2	3	CH_2CH_2Cl	CH_2CH_2Cl	0	H	H	0	H	2HCl
302	(5)	N	2	4-H	5-NHEt	H	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	2HCl
303	(5)	N	2	4-H	5-NH^{n}Pr	H	2-H	4-H	5-CO_2H	6-H	3	CH_2CH_2Br	CH_2CH_2Br	0	H	H	0	H	2HCl
304	(5)	N	2	4-H	5-OH	H	2-H	3-CO_2Me	5-H	6-H	4	H	H	1	Me	Me	0	CHO	HCl
305	(5)	N	2	4-H	5-OMe	H	2-H	3-CO_2Et	5-H	6-H	4	H	H	1	Et	Et	0	CO_2Me	HCl
306	(5)	N	2	4-H	5-OEt	CO_2Me	2-H	3-H	5-CN	6-H	4	H	H	0	H	H	1	CO_2Et	HCl
307	(5)	N	2	4-H	5-Me	H	2-H	3-H	5-H	6-CHO	4	H	H	0	H	H	1	H	2HCl
308	(5)	N	4	2-Me	5-H	H	3-$CONH_2$	4-H	5-H	6-H	2	$CO_2{}^tBu$	$CO_2{}^tBu$	1	H	H	0	H	
309	(5)	N	4	2-Et	5-H	H	3-H	4-CONHMe	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
310	(5)	N	4	2-^{n}Pr	5-H	CO_2Et	3-CH_2OH	4-H	5-H	6-H	2	Me	Me	0	H	H	1	H	2HCl
311	(5)	N	4	2-H	5-SMe	H	3-H	4-CH_2Cl	5-H	6-H	2	H	H	0	CH_2CH_2OH	CH_2CH_2OH	1	H	2HCl
312	(5)	N	4	2-H	5-SEt	H	3-H	4-H	5-H	6-H	2	H	H	0	H	H	1	H	2HCl
313	(5)	N→O	2	4-Me	5-H	H	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	HCl
314	(5)	N→O	2	4-Et	5-H	$CO_2{}^tBu$	2-H	4-H	5-H	6-CHO	3	H	H	0	H	H	0	H	HCl
315	(5)	N→O	2	4-^{n}Pt	5-H	H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

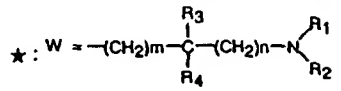
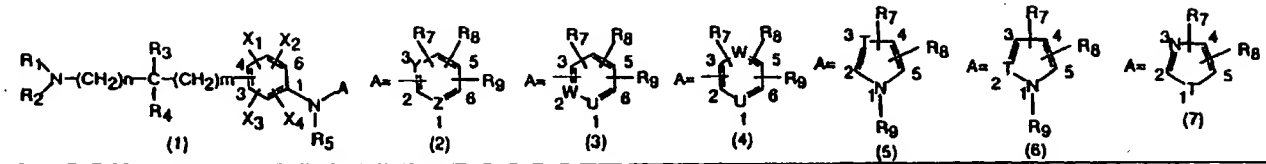
★: W = 

Table 22



Ex. No.	A	N	W	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
316	(4)	N	N	3	2-NO_2	5-H	6-Me	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
317	(4)	N	N	3	2-NO_2	5-H	6-H	2-Me	4-H	5-H	6-H	3	H	Me	0	H	H	0	H	HCl
318	(4)	N	N	3	2-CO_2H	5-H	6-Et	2-H	4-OMe	5-H	6-H	3	Ac	H	0	H	H	0	H	
319	(4)	N	N	3	2-CO_2H	5-H	6-H	2-Et	4-H	5-H	6-H	3	H	Et	0	H	H	0	H	HCl
320	(4)	N	N	3	2-CO_2Me	5-H	6-^{n}Pr	2-H	4-OEt	5-H	6-H	3	Bz	H	0	H	H	0	H	
321	(4)	N	N	3	2-CO_2Et	5-H	6-H	2-^{n}Pr	4-H	5-H	6-H	3	H	^{n}Pr	0	H	H	0	H	HCl
322	(4)	N	N	3	2-$CO_2{}^n$Pr	5-H	6-^{n}Bu	2-H	4-O^{n}Pr	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
323	(4)	N	N	3	2-CN	5-H	6-OH	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
324	(4)	N	N	3	2-CN	5-H	6-H	2-H	4-H	5-NH_2	6-H	3	H	H	0	Et	H	0	H	2HCl
325	(4)	N	N	3	2-H	5-NH_2	6-H	2-H	4-H	5-NHMe	6-H	3	H	H	0	H	H	0	H	2HCl
326	(4)	N	N	3	2-H	5-NHAc	6-H	2-H	4-H	5-NHEt	6-H	3	H	H	0	CH_2CH_2Cl	CH_2CH_2Cl	0	H	2HCl
327	(4)	N	N	3	2-H	5-NHBz	6-H	2-H	4-SMe	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
328	(4)	N	N	3	2-$CONH_2$	5-H	6-H	2-H	4-SEt	5-H	6-H	3	CO_2Me	H	0	H	H	0	H	
329	(4)	N	N	3	2-CONHMe	5-H	6-H	2-H	4-H	5-H	6-H	3	CH_2CH_2Br	CH_2CH_2Br	0	H	H	0	H	2HCl
330	(4)	N	N	3	2-H	5-H	6-Me	2-H	4-H	5-H	6-NO_2	3	H	H	0	CH_2OH	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

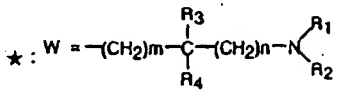
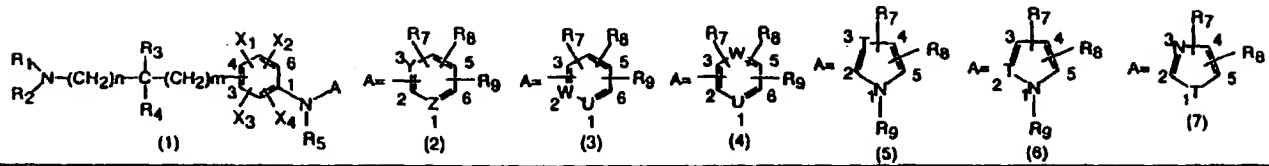


Table 23



Ex. No.	A	U	W	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
331	(4)	N	N	3	2-H	5-H	6-Et	2-H	3-H	5-H	6-CO_2H	4	Me	Me	1	H	H	0	Me	2HCl
332	(4)	N	N	3	2-H	5-H	6-^{n}Pr	2-H	3-H	5-H	6-CO_2Me	4	H	H	1	H	H	0	H	2HCl
333	(4)	N	N	3	2-H	5-H	6-^{n}Bu	2-H	3-H	5-H	6-CO_2Et	4	H	H	1	H	H	0	Et	2HCl
334	(4)	N	N	3	2-H	5-OH	6-H	2-H	3-H	5-CN	6-H	4	H	H	0	Me	Me	1	H	2HCl
335	(4)	N	N	3	2-H	5-OMe	6-H	2-H	3-H	5-F	6-H	4	H	H	0	H	H	1	^{n}Pr	2HCl
336	(4)	N	N	3	2-H	5-OEt	6-H	2-H	3-H	5-H	6-CO_2NH_2	4	H	H	0	H	H	1	H	2HCl
337	(4)	N	N	3	2-SMe	5-H	6-H	2-Cl	3-H	4-H	5-H	6	H	H	0	H	H	1	Ac	HCl
338	(4)	N	N	3	2-Et	5-H	6-H	2-CH_2OH	3-H	4-H	5-H	6	H	H	0	H	H	1	H	2HCl
339	(4)	N	N	3	2-CF_3	5-H	6-H	2-H	3-H	4-H	5-CO_2NHMe	6	H	H	0	H	H	1	Bz	HCl
340	(4)	N	N	3	2-CF_3	5-H	6-H	2-H	3-H	4-H	5-cyclopentyl	6	H	H	1	H	H	0	H	2HCl
341	(4)	N	N	3	2-H	5-H	6-pyrrolidin-1-yl	2-H	3-H	4-H	5-H	6	H	H	1	H	H	0	$CO_2{}^t$Bu	
342	(4)	N	N	3	2-H	5-H	6-piperidino	2-H	3-H	4-H	5-H	6	H	H	1	H	H	0	H	2HCl
343	(4)	N→I	N→I	3	2-H	5-H	6-cyclobutyl	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
344	(4)	N→I	N→I	3	2-H	5-H	6-H	2-H	3-H	5-H	6-cyclohexylthio	4	H	H	1	H	H	0	H	2HCl
345	(4)	N→I	N→I	3	2-H	5-H	6-H	2-H	3-H	4-Bn	5-H	6	H	H	0	H	H	1	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

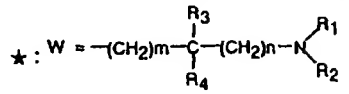
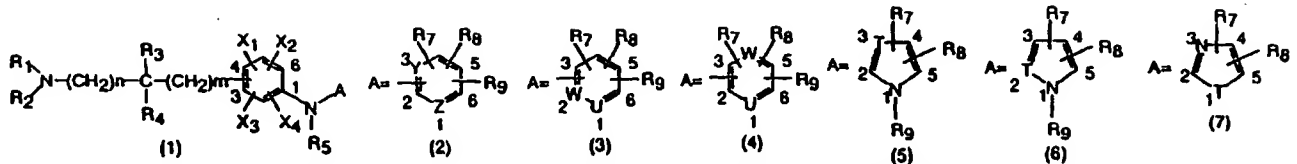


Table 24



Ex. No.	A	U	W	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
346	(3)	N	N	3	4-NO_2	5-H	6-H	2-Me	4-H	5-H	6-H	3	Me	H	0	H	H	0	H	HCl
347	(3)	N	N	3	4-NO_2	5-H	6-H	2-Et	4-H	5-H	6-H	3	H	H	0	H	H	0	Me	HCl
348	(3)	N	N	3	4-H	5-CO_2H	6-H	2-H	4-^{n}Bu	5-H	6-H	3	Et	H	0	H	H	0	H	HCl
349	(3)	N	N	3	4-H	5-CO_2Me	6-H	2-H	4-Bn	5-H	6-H	3	H	H	0	H	H	0	Et	HCl
350	(3)	N	N	3	4-H	5-H	6-$CONH_2$	2-H	4-H	5-NH_2	6-H	3	Bn	H	0	H	H	0	H	
351	(3)	N	N	3	4-H	5-H	6-CONHMe	2-H	4-H	5-NHMe	6-H	3	H	H	0	H	H	0	Ac	HCl
352	(3)	N	N	3	4-CF_3	5-H	6-H	2-F	4-H	5-H	6-H	3	H	H	0	Me	Me	0	H	2HCl
353	(3)	N	N	3	4-CF_3	5-H	6-H	2-H	4-Br	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
354	(3)	N	N	3	4-H	5-CN	6-H	2-Cl	4-H	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
355	(3)	N	N	3	4-H	5-CN	6-H	2-H	4-NHBn	5-H	6-H	3	H	H	0	H	H	0	H	HCl
356	(3)	N	N	3	4-NH_2	5-H	6-H	2-H	4-OMe	5-H	6-H	3	Ac	H	0	H	H	0	H	·
357	(3)	N	N	3	4-H	5-NHMe	6-H	2-H	4-H	5-OEt	6-H	3	H	H	0	H	H	0	Bz	2HCl
358	(3)	N	N	3	4-H	5-H	6-NHBn	2-^{n}Pr	4-H	5-H	6-H	3	CO_2Me	H	0	H	H	0	H	
359	(3)	N	N	3	4-^{n}Pr	5-H	6-H	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	2HCl
360	(3)	N	N	3	4-H	5-Et	6-H	2-H	4-H	5-H	6-CHO	3	$CO_2{}^t$Bu	H	0	H	H	0	H	

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

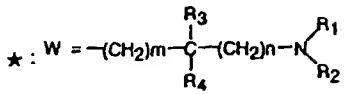
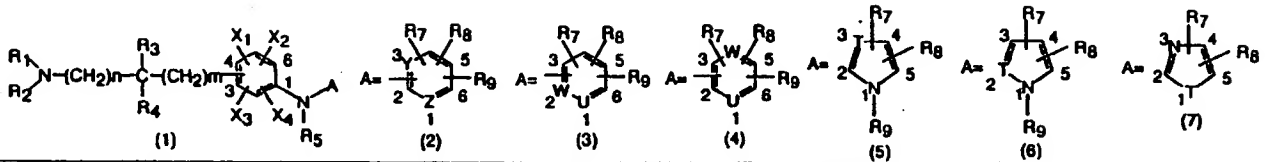


Table 25



Ex. No.	A	U	W	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
361	(3)	N	N	3	4-Me	5-H	6-H	2-H	4-CO_2H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
362	(3)	N	N	3	4-SMe	5-H	6-H	2-H	4-H	5-CO_2Et	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	$CO_2{}^tBu$	
363	(3)	N	N	3	4-H	5-SEt	6-H	2-H	4-H	5-H	6-$CONH_2$	3	H	H	0	H	H	0	H	2HCl
364	(3)	N	N	3	4-H	5-H	6-S^{n}Pr	2-H	4-H	5-CONHMe	6-H	3	H	H	0	H	H	0	H	2HCl
365	(3)	N	N	3	4-F	5-H	6-H	2-CN	3-H	5-pyrrolidin-1-yl	6-H	4	H	H	1	H	H	0	Me	2HCl
366	(3)	N	N	3	4-H	5-Br	6-H	2-H	3-H	5-piperidino	6-H	4	H	H	0	H	H	1	H	2HCl
367	(3)	N→O	N→O	3	4-H	5-H	6-Me	2-H	3-H	5-H	6-H	4	H	H	1	H	H	0	H	HCl
368	(3)	N→O	N→O	3	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
369	(3)	N	N	4	3-OMe	5-H	6-H	2-F	4-H	5-H	6-H	3	Et	H	0	H	H	0	H	2HCl
370	(3)	N	N	4	3-H	5-OEt	6-H	2-H	3-Cl	5-H	6-H	3	H	H	0	Et	H	0	H	2HCl
371	(3)	N	N	4	3-H	5-H	6-O^{n}Pr	2-H	3-H	5-Br	6-H	3	H	H	0	H	H	0	H	2HCl
372	(3)	N	N	4	3-NO_2	5-H	6-OMe	2-H	3-H	4-CH_2CH_2Ph	5-H	6	H	H	1	H	H	0	H	HCl
373	(3)	N	N	4	3-H	5-H	6-H	2-H	3-H	4-$CH_2(CH_2)_2$Ph	5-H	6	H	H	1	CH_2OH	H	0	H	2HCl
374	(3)	N→O	N→O	4	3-H	5-H	6-NHMe	2-H	3-H	4-H	5-H	6	H	H	0	H	H	1	CO_2Et	2HCl
375	(3)	N→O	N→O	4	3-H	5-H	6-NHEt	2-H	3-H	5-H	6-H	3	H	H	0	H	H	1	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

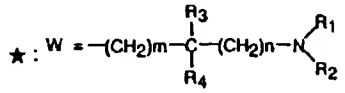
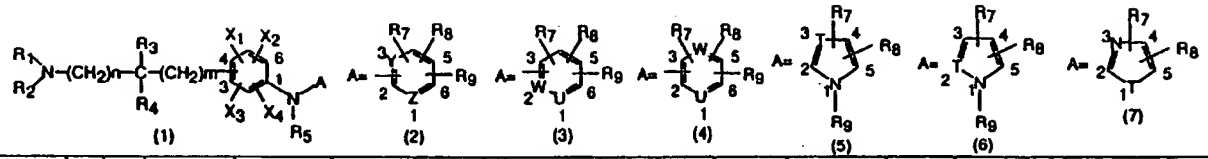


Table 26



Ex. No.	Q	T	Substitution position of A	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of R_9	R_1	R_2	n	R_3	R_4	m	R_5	salt
376	(6)	N	3	4-NO_2	5-H	H	2-H	4-Me	5-H	6-H	3	Me	H	0	H	H	0	Me	2HCl
377	(6)	N	3	4-NO_2	5-H	Me	2-H	4-Et	5-H	6-H	3	H	H	0	Me	Me	0	H	2HCl
378	(6)	N	3	4-CF_3	5-H	H	2-H	4-^{n}Pr	5-H	6-H	3	H	H	0	Me	H	0	H	HCl
379	(6)	N	3	4-CF_3	5-H	Et	2-CH_2OH	4-H	5-H	6-H	3	Et	H	0	H	H	0	H	HCl
380	(6)	N	3	4-H	5-CO_2H	H	2-CH_2CH_2OH	4-H	5-H	6-H	3	H	H	0	H	H	0	Et	HCl
381	(6)	N	3	4-H	5-CO_2Me	^{n}Pr	2-H	4-H	5-H	6-H	3	H	H	0	Et	H	0	H	HCl
382	(6)	N	3	4-H	5-CO_2Et	H	2-H	4-H	5-NH_2	6-H	3	^{n}Pr	H	0	H	H	0	H	2HCl
383	(6)	N	3	4-CN	5-H	H	2-H	4-H	5-H	6-NHMe	3	H	H	0	H	H	0	Ac	2HCl
384	(6)	N	3	4-$CONH_2$	5-H	H	2-NHEt	4-H	5-H	6-H	3	H	H	0	CH_2OH	H	0	H	2HCl
385	(6)	N	3	4-CONHMe	5-H	H	2-H	4-H	5-H	6-H	3	Ac	H	0	H	H	0	H	
386	(6)	N	3	4-H	5-H	Ac	2-Cl	4-H	5-H	6-H	3	H	H	0	CH_2CH_2OH	CH_2CH_2OH	0	H	HCl
387	(6)	N	3	4-H	5-H	Bn	2-Br	4-H	5-H	6-H	3	H	H	0	Et	Et	0	H	HCl
388	(6)	N	3	4-H	5-H	CO_2Me	2-OMe	4-H	5-H	6-H	3	H	H	0	H	H	0	Bn	HCl
389	(6)	N	3	4-H	5-H	CO_2Et	2-H	4-OEt	5-H	6-H	3	CO_2^tBu	CO_2^tBu	0	H	H	0	H	
390	(6)	N	3	4-H	5-H	CO_2^nPr	2-H	4-OBn	5-H	6-H	3	H	H	0	Bn	H	0	Bz	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

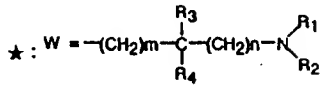
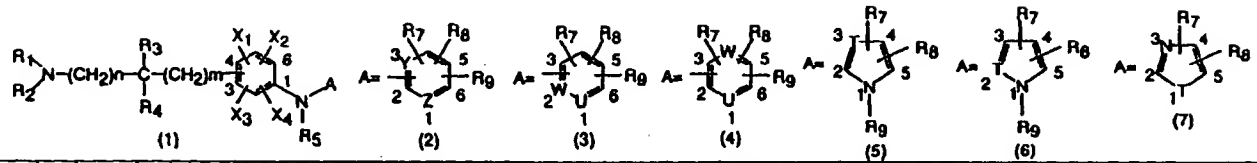


Table 27



Ex. No.	Q	T	Substitution position of A	R_{11}*1	R_{12}*1	R_{13}*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
391	(6)	N	3	4-OMe	5-H	Bz	2-H	4-H	5-H	6-NO_2	3	H	H	0	H	H	0	H	HCl
392	(6)	N	3	4-OEt	5-H	H	2-H	4-H	5-H	6-CO_2Me	3	Me	Me	0	H	H	0	H	2HCl
393	(6)	N	3	4-O^{n}Pr	5-H	H	2-H	4-H	5-H	6-CO_2Et	3	H	H	0	H	H	0	CO_2Me	2HCl
394	(6)	N	3	4-H	5-SMe	H	2-H	3-H	5-$CONH_2$	6-H	4	H	H	1	H	H	0	H	2HCl
395	(6)	N	3	4-H	5-SEt	H	2-H	3-H	5-CONHMe	6-H	4	H	H	1	H	H	0	H	2HCl
396	(6)	N	4	3-H	5-S^{n}Bu	H	2-H	3-H	5-CONHEt	6-H	4	H	H	0	Me	H	1	H	2HCl
397	(6)	N	4	3-F	5-H	H	2-H	3-H	5-H	6-H	4	CH_2CH_2Br	CH_2CH_2Br	0	H	H	1	H	2HCl
398	(6)	N	4	3-Cl	5-H	H	2-H	4-SMe	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
399	(6)	N	4	3-Br	5-H	H	2-H	4-SEt	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
400	(6)	N	4	3-NH_2	5-H	H	2-H	3-H	4-H	5-CHO	6	H	H	1	H	H	0	H	2HCl
401	(6)	N	4	3-NHMe	5-H	H	2-H	3-H	4-$NHCO_2$Me	5-H	6	H	H	1	H	H	0	H	2HCl
402	(6)	N→O	4	3-H	5-Me	H	2-H	3-OBn	4-H	5-H	6	$-CH_2(CH_2)_2CH_2-$		1	H	H	0	H	HCl
403	(6)	N→O	4	3-H	5-Et	H	2-H	4-H	5-H	6-H	3	H	H	1	$-CH_2(CH_2)_3CH_2-$		0	H	HCl
404	(6)	N→O	3	4-H	5-OMe	H	2-H	4-NHBn	5-H	6-H	3	H	H	1	H	H	0	H	2HCl
405	(6)	N→O	3	4-H	5-OEt	H	2-H	3-H	5-H	6-H	4	H	H	1	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

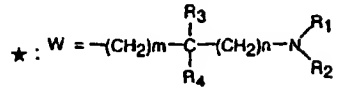
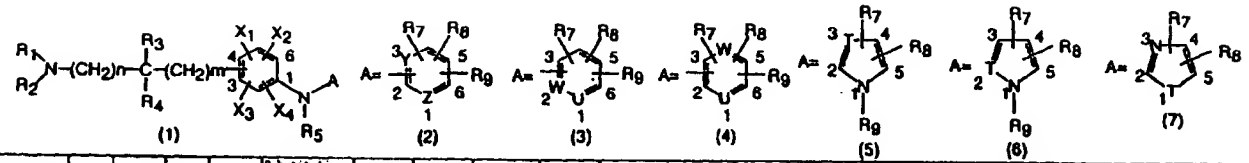


Table 28



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5
406	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-Me	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
407	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-pyrrolidin-1-yl	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
408	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	3-H	5-H	6-H	4	$CO_2{}^tBu$	H	1	H	H	0	H
409	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-OMe	3	$CO_2{}^tBu$	H	0	H	H	0	H
410	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	Me	Me	0	H
411	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-Me	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
412	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	3-H	4-H	5-H	6-H	2	$CO_2{}^tBu$	H	1	H	H	0	H
413	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OMe	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
414	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Cl	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
415	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Me	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
416	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-F	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
417	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OEt	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
418	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
419	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
420	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

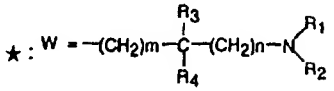
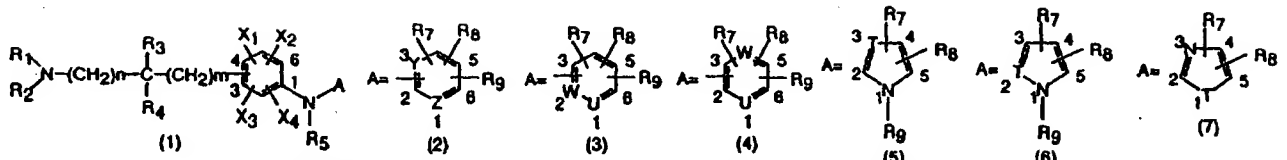


Table 29



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5
421	(2)	CR_6	N	H	2	4-H	5-NO_2	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
422	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
423	(2)	CR_6	N	H	2	4-CO_2Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
424	(2)	CR_6	N	-	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
425	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OEt	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
426	(2)	CR_6	N	CF_3	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
427	(2)	CR_6	CH	NO_2	2	4-H	5-OMe	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
428	(2)	CR_6	CMe	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
429	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	Me	Me	0	H
430	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	Et	H	0	H
431	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-Me	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
432	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-Et	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
433	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-OEt	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
434	(2)	CR_6	N	H	2	4-Me	5-H	6-H	3-H	4-H	5-H	6-H	2	$CO_2{}^tBu$	H	1	H	H	0	H
435	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-Cl	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

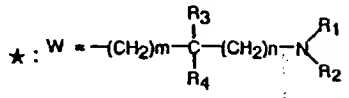
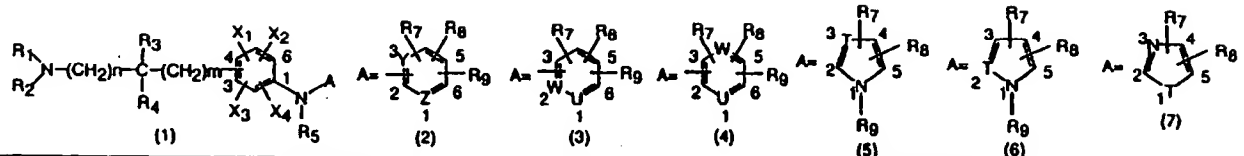


Table 30



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5
436	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	$-CH_2CH_2CH_2-$		0	H
437	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	3-H	5-H	6-H	4	$CO_2{}^tBu$	H	1	H	H	0	H
438	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
439	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-Cl	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
440	(2)	CR_6	N	CN	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
441	(2)	CR_6	N	Cl	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
442	(2)	CR_6	N	CO_2Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
443	(2)	CR_6	N	H	2	4-CO_2H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
444	(2)	CR_6	N	H	2	4-CH_2OH	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
445	(2)	CR_6	N	H	2	4-Me	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
446	(2)	CR_6	N	NO_2	2	4-H	5-H	6-$CH(CO_2Me)_2$	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
447	(2)	CR_6	N	NO_2	2	4-H	5-H	6-$CMe(CO_2Et)_2$	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H
448	(2)	CR_6	N	NO_2	2	4-H	5-H	6-SMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
449	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H
450	(2)	CR_6	N	H	2	4-Me	5-H	6-Me	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

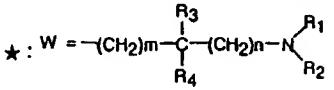
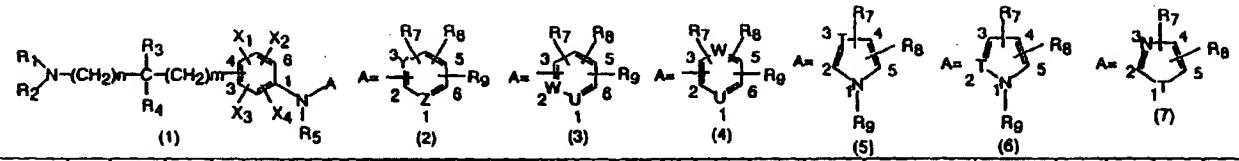


Table 31

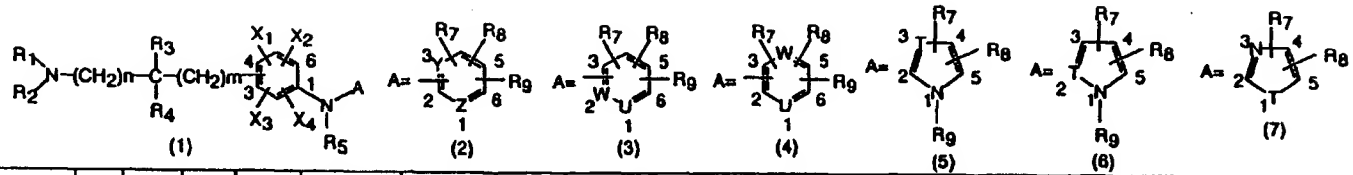


Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
451	(2)	CR_6	N	H	2	4-Et	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
452	(2)	CR_6	N	CO_2H	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
453	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
454	(2)	CR_6	N	CH_2OH	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
455	(2)	CR_6	N	Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
456	(2)	CR_6	N	CHO	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
457	(2)	CR_6	N	H	2	4-H	5-NO_2	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
458	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-Me	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
459	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-pyrrolidin-1-yl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
460	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	3-H	5-H	6-H	4	H	H	1	H	H	0	H	HCl
461	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-OMe	3	H	H	0	H	H	0	H	HCl
462	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	Me	Me	0	H	HCl
463	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-Me	6-H	3	H	H	0	H	H	0	H	HCl
464	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	HCl
465	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OMe	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★: W = $-(CH_2)m-C(R_3)(R_4)-(CH_2)n-N(R_1)(R_2)$

Table 32



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
466	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Cl	5-H	6-H	3	H	H	0	H	H	0	H	HCl
467	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-F	5-H	6-H	3	H	H	0	H	H	0	H	HCl
468	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-OEt	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
469	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-Cl	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
470	(2)	CR_6	N	H	2	4-CO_2Me	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
471	(2)	CR_6	N	H	2	4-CO_2H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
472	(2)	CR_6	N	H	2	4-CH_2OH	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
473	(2)	CR_6	N	H	2	4-Me	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
474	(2)	N	N	-	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
475	(2)	CR_6	N	CF_3	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
476	(2)	CR_6	CH	NO_2	2	4-H	5-OMe	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
477	(2)	CR_6	CMe	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
478	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
479	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	Me	Me	0	H	2HCl
480	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	Et	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

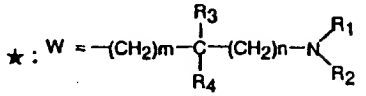
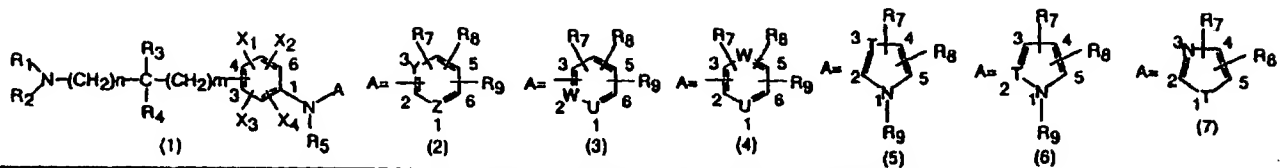
★: 

Table 33



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
481	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-Me	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
482	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-Et	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
483	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-OEt	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
484	(2)	CR_6	N	H	2	4-Me	5-H	6-H	3-H	4-H	5-H	6-H	2	H	H	1	H	H	0	H	2HCl
485	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-Cl	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
486	(2)	CR_6	N	H	2	4-Me	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
487	(2)	CR_6	N	H	2	4-Et	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
488	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	$-CH_2CH_2CH_2-$		0	H	2HCl
489	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	3-H	5-H	6-H	4	H	H	1	H	H	0	H	2HCl
490	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
491	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-Cl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
492	(2)	CR_6	N	CN	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
493	(2)	CR_6	N	Cl	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
494	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
495	(2)	CR_6	N	Me	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

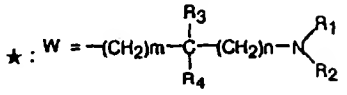
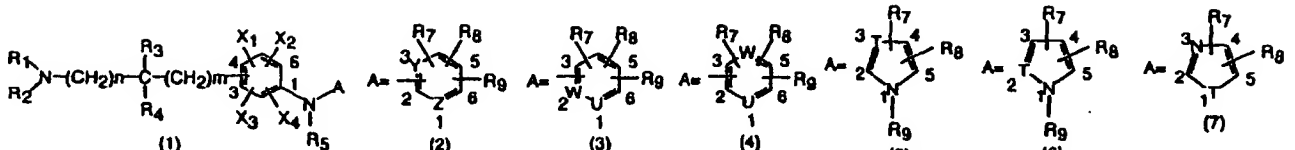


Table 34



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ⁂	R_1	R_2	n	R_3	R_4	m	R_5	salt
496	(2)	CR_6	CH	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	HCl
497	(2)	CR_6	N	H	2	4-H	5-Me	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
498	(2)	CR_6	N	Me	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
499	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-OMe	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
500	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-pyrazol-1-yl	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
501	(2)	CR_6	N	H	2	4-H	5-Me	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
502	(2)	CR_6	N	Me	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
503	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
504	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-H	4-pyrazol-1-yl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
505	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{n}Pr	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
506	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{n}Pr	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
Ex. No.	A	T	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ⁂	R_1	R_2	n	R_3	R_4	m	R_5	salt
507	(7)	S	-	-	2	4-H	5-Me	-	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
508	(7)	S	-	-	2	4-H	5-Me	-	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	
509	(7)	S	-	-	2	4-Me	5-H	-	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
510	(7)	S	-	-	2	4-Me	5-H	-	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

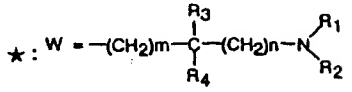
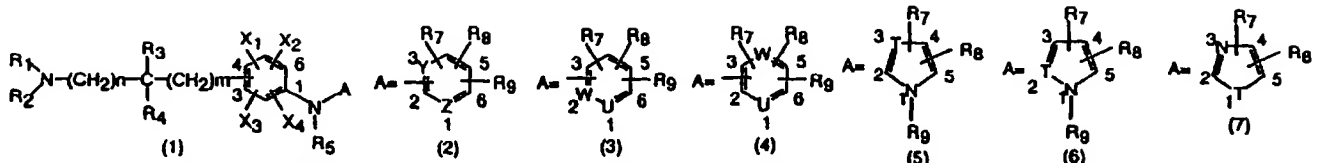


Table 35



Ex. No.	A	T	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
511	(7)	O	-	-	2	4-H	5-Me	-	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
512	(7)	O	-	-	2	4-H	5-Me	-	2-OEt	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
513	(7)	O	-	-	2	4-H	5-Me	-	2-Me	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
514	(7)	O	-	-	2	4-H	5-Me	-	2-H	4-OMe	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
515	(7)	O	-	-	2	4-H	5-Me	-	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	CF_3CO_2H
516	(7)	O	-	-	2	4-H	5-Me	-	2-OEt	4-H	5-H	6-H	3	H	H	0	H	H	0	H	CF_3CO_2H
517	(7)	O	-	-	2	4-H	5-Me	-	2-Me	4-H	5-H	6-H	3	H	H	0	H	H	0	H	CF_3CO_2H
518	(7)	O	-	-	2	4-H	5-Me	-	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	CF_3CO_2H
Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
519	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-Cl	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
520	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-Me	5-H	6-H	3	$CO_2{}^tBu$	H	0	H	H	0	H	
521	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-Cl	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
522	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OEt	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
523	(2)	CR_6	N	NO_2	2	4-H	5-NO_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	
524	(2)	CR_6	N	CN	2	4-Me	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	
525	(2)	CR_6	N	H	2	4-CN	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

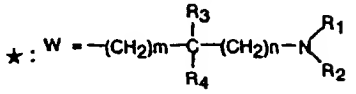
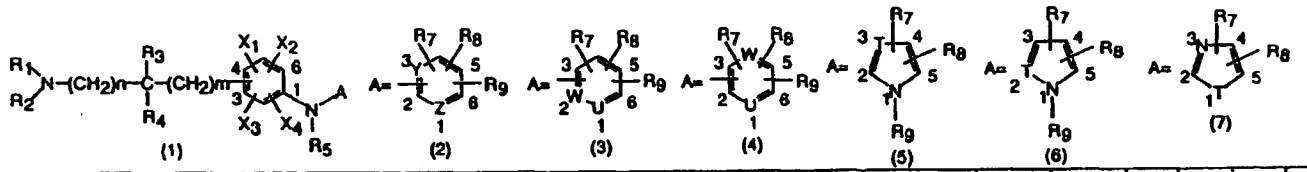


Table 36



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5
526	(2)	CR_6	N	H	2	4-H	5-CN	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
527	(2)	CR_6	N	CN	2	4-CO_2Et	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
528	(2)	CR_6	N	H	2	4-CO_2H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
529	(2)	CR_6	N	H	2	4-H	5-CO_2H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
530	(2)	CR_6	N	Cl	2	4-H	5-CO_2H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
531	(2)	CR_6	N	H	2	4-CO_2H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
532	(2)	CR_6	N	H	2	4-H	5-H	6-CO_2H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
533	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
534	(2)	CR_6	N	$CONH_2$	2	4-H	5-Cl	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
535	(2)	CR_6	N	H	2	4-$CONH_2$	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
536	(2)	CR_6	N	$CONH_2$	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
537	(2)	CR_6	N	H	2	4-H	5-Br	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
538	(2)	CR_6	N	Cl	2	4-H	5-Cl	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
539	(2)	CR_6	N	H	2	4-H	5-H	6-Me	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H
540	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OMe	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

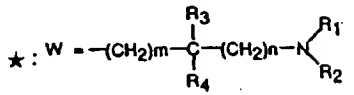
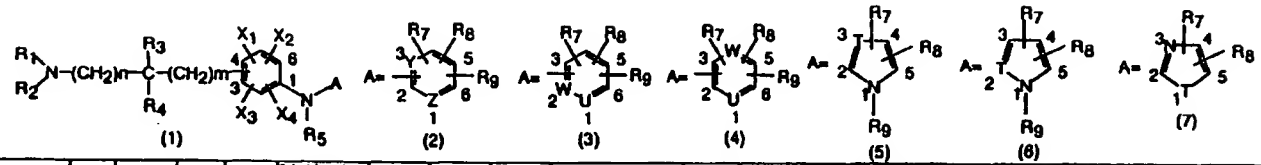
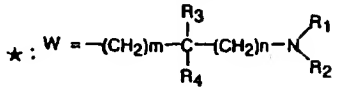
★: W = 

Table 37



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of B	R_1	R_2	n	R_3	R_4	m	R_5	salt
541	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OMe	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
542	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{i}Pr	4-H	5-H	6-H	3	$CO_2{}^t$Bu	$CO_2{}^t$Bu	0	H	H	0	H	
543	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{i}Pr	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
544	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{n}Bu	4-H	5-H	6-H	3	$CO_2{}^t$Bu	H	0	H	H	0	H	
545	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{n}Bu	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
546	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{t}Bu	4-H	5-H	6-H	3	$CO_2{}^t$Bu	H	0	H	H	0	H	
547	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{t}Bu	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
548	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OCH_2Ph	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
549	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OCH_2CH_2Ph	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
550	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-Et	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
551	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-CH_2Ph	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
552	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-OMe	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
553	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{i}Pr	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
554	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{n}Bu	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
555	(2)	CR_6	N	H	2	4-Me	5-H	6-H	2-O^{t}Bu	4-Me	5-H	6-H	3	H	H	0	H	H	0	H	2HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.



Example 1

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-3-nitropyridine

[0055] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (1.50 g), triethylamine (2.0 ml), 2-chloro-3-nitropyridine (1.10 g) and anhydrous dimethylformamide (15 ml) was stirred at 60°C for 20 h and, thereafter, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 3 : 1) to give 1.42 g of the titled compound (yield, 69%).

^{1}H-NMR($CDCL_3$)
δ:1.47(18H, s), 4.81(2H, s), 6.83(1H, dd, J=8.3, 4.3Hz), 7.11(1H, d, J=7.9Hz), 7.34(1H, dd, J=7.9, 7.9Hz), 7.55-7.63 (2H, m), 8.47(1H, dd, J=4.3, 1.7Hz), 8.53(1H, dd, J=8.3, 1.7Hz), 10.11(1H, brs)

[0056] The procedure of Example 1 was repeated using corresponding aniline derivatives or corresponding halogenated derivatives to give the compounds shown in Tables 38 - 43 (under "Reaction condition" in the tables, base:(1) is triethylamine and base:(2) is diisopropylethylamine).

Table 38

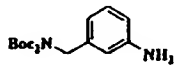
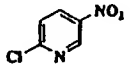
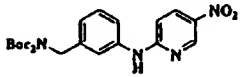
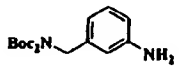
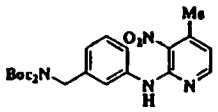
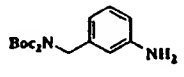
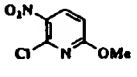
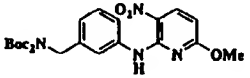
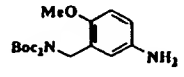
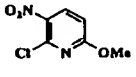
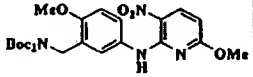
Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
9				base : (1)	^{1}H-NMR($CDCl_3$) δ 1.47(18H, s), 4.80(2H, s), 6.77(1H, d, J=9.2Hz), 7.16(1H, d, J=7.3Hz), 7.26-7.39(3H, m), 8.23(1H, dd, J=9.2, 2.6Hz), 9.08 (1H, d, J=2.6Hz)
13				base : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(18H, s), 2.57(3H, s), 4.79(2H, s), 6.66(1H, d, J=5.0Hz), 7.06(1H, d, J=7.6Hz), 7.26-7.33(1H, m), 7.33(1H, dd, J=7.6, 7.6Hz), 7.46(1H, s), 8.18(1H, dd, J=5.0Hz), 9.14(1H, brs)
17				base : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(18H, s), 3.96(3H, s), 4.80(2H, s), 6.23(1H, d, J=9.2Hz), 7.40(1H, d, J=7.6Hz), 7.32(1H, dd, J=7.6, 7.6Hz), 7.56(1H, d, J=7.6Hz), 7.60(1H, s), 8.42(1H, d, J=9.2Hz), 10.63(1H, brs)
21				base : (1)	^{1}H-NMR($CDCl_3$) δ 1.45(18H, s), 3.85(3H, s), 3.90(3H, s), 4.84(2H, s), 6.17(1H, d, J=9.2Hz), 6.85(1H, d, J=8.6Hz), 7.34(1H, d, J=2.3Hz), 7.46(1H, dd, J=8.6, 2.3Hz), 8.39(1H, d, J=9.2Hz), 10.50(1H, brs)

Table 39

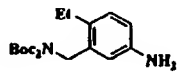
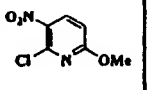
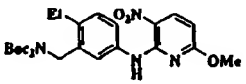
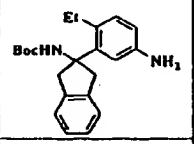
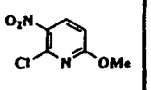
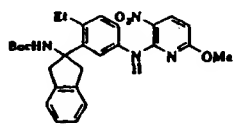
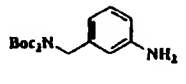
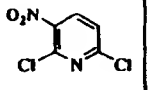
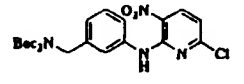
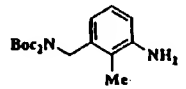
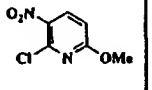
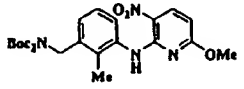
Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
23				base : (I)	^{1}H-NMR($CDCl_3$) δ 1.24(3H, t, J=7.3Hz), 1.45(18H, s), 2.69(2H, q, J=7.3Hz), 3.94(3H, s), 4.85(2H, s), 6.19(1H, d, J=8.9Hz), 7.18(1H, d, J=8.3Hz), 7.32(1H, d, J=2.0Hz), 7.54(1H, dd, J=8.3, 2.0 Hz), 8.40(1H, d, J=8.9Hz)
25				base : (I)	^{1}H-NMR($CDCl_3$) δ 1.30(3H, t, J=7.3Hz), 1.30(9H, s), 2.85(2H, q, J=7.3Hz), 3.59(4H, s), 3.92(3H, s), 5.07(1H, brs), 6.18(1H, d, J=8.9Hz), 7.18-7.29(5H, m), 7.43(1H, s), 7.73(1H, dd, J=8.6, 2.0Hz), 8.40(1H, d, J=8.9Hz), 10.58(1H, brs)
27				base : (I)	^{1}H-NMR($CDCl_3$) δ 1.47(18H, s), 4.81(2H, s), 6.80(1H, d, J=8.6Hz), 7.13(1H, d, J=7.6Hz), 7.36(1H, dd, J=7.6, 7.6Hz), 7.49(1H, s), 7.65(1H, d, J=7.6Hz), 8.46(1H, d, J=8.6Hz), 10.24(1H, brs)
406				base : (I)	^{1}H-NMR($CDCl_3$) δ 10.33(1H, brs), 8.40(1H, d, J=8.9Hz), 7.61(1H, d, J=7.9Hz), 7.21(1H, dd, J=7.9, 7.6Hz), 7.05(1H, d, J=7.6Hz), 6.18(1H, d, J=8.9Hz), 4.85(2H, s), 3.76(3H, s), 2.27(3H, s), 1.45(18H, s) FAB-MS(m/z) 489(M$^+$+1)

Table 40

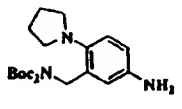
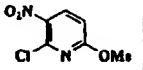
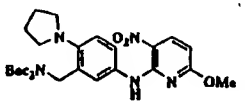
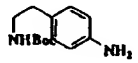
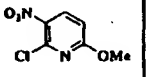
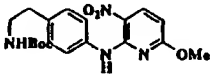
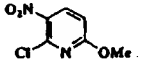
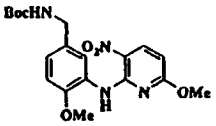
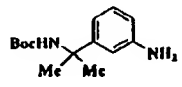
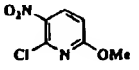
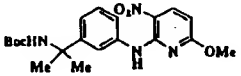
Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
407				base : (1)	^{1}H-NMR($CDCl_3$) δ 10.54(1H, brs), 8.39(1H, d, J=9.2Hz), 7.45 (1H, dd, J=8.6, 2.3Hz), 7.30-7.24(1H, m), 6.98(1H, d, J=8.6Hz), 6.16(1H, d, J=9.2Hz), 4.85(2H, s), 3.92(3H, s), 3.10(4H, t, J=5.4Hz), 1.94(4H, t, J=5.4Hz), 1.41(18H, s) FAB-MS(m/z) 544(M$^+$+1)
408				base : (1)	^{1}H-NMR($CDCl_3$) δ 10.62(1H, brs), 8.42(1H, d, J=8.9Hz), 7.60 (2H, d, J=8.6Hz), 7.21(2H, d, J=8.6Hz), 6.22(1H, d, J=8.9Hz), 4.57(1H, brs), 3.96(3H, s), 3.39(2H, dt, J=6.9, 6.9Hz), 2.81(2H, t, J=6.9Hz), 1.44(9H, s) FAB-MS(m/z) 389(M$^+$+1)
409				base : (1)	^{1}H-NMR($CDCl_3$) δ 11.20(1H, brs), 8.56(1H, d, J=2.0Hz), 8.44 (1H, d, J=9.2Hz), 7.00(1H, dd, J=8.3, 2.0Hz), 6.90(1H, d, J=8.3Hz), 6.23(1H, d, J=9.2Hz), 4.75(1H, brs), 4.29(2H, d, J=5.6Hz), 4.06(3H, s), 3.96(3H, s), 1.46(9H, s) FAB-MS(m/z) 405(M$^+$+1)
410				base : (1)	^{1}H-NMR($CDCl_3$) δ 10.68(1H, brs), 8.41(1H, d, J=8.9Hz), 7.65 (1H, s), 7.58(1H, t, J=7.9Hz), 7.33(1H, t, J=7.9Hz), 7.22(1H, d, J=7.9Hz), 6.22(1H, d, J=8.9Hz), 4.97(1H, s), 3.98(3H, s), 1.65(9H, s), 1.38(6H, brs) FAB-MS(m/z) 403(M$^+$+1)

Table 41

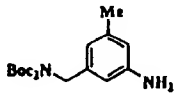
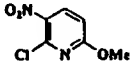
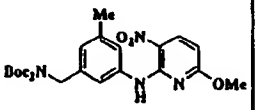
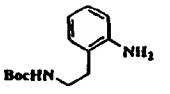
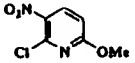
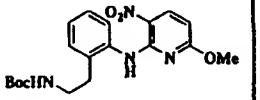
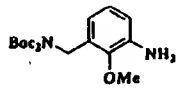
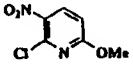
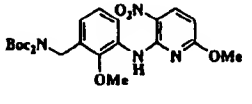
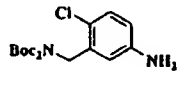
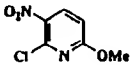
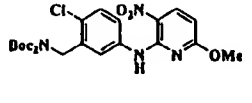
Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
411				base: (1)	^{1}H-NMR($CDCl_3$) δ 10.60(1H, br), 8.40(1H, d, J=8.9Hz), 7.44(1H, s), 7.37(1H, s), 6.92(1H, s), 6.21(1H, d, J=8.9Hz), 4.76(2H, s), 3.97(3H, s), 2.35(3H, s), 1.46(18H, s) FAB-MS(m/z) 489(M$^+$+1)
412				base: (1)	^{1}H-NMR($CDCl_3$) δ 10.45(1H, brs), 8.41(1H, d, J=9.2Hz), 7.83(1H, d, J=7.3Hz), 7.31-7.25(2H, m), 7.21(1H, d, J=7.3Hz), 6.20(1H, d, J=9.2Hz), 4.67(1H, brs), 3.81(3H, s), 3.39(2H, dt, J=6.9, 6.9Hz), 2.89(2H, t, J=6.9Hz), 1.39(9H, s) FAB-MS(m/z) 389(M$^+$+1)
413				base: (1)	^{1}H-NMR($CDCl_3$) δ 11.24(1H, brs), 8.45(1H, d, J=9.2Hz), 8.42(1H, d, J=7.9Hz), 7.12(1H, dd, J=7.9, 7.6Hz), 6.95(1H, d, J=7.6Hz), 6.26(1H, d, J=9.2Hz), 4.94(2H, s), 4.04(3H, s), 3.87(3H, s), 1.46(18H, s) FAB-MS(m/z) 505(M$^+$+1)
414				base: (1)	^{1}H-NMR($CDCl_3$) δ 10.59(1H, brs), 8.41(1H, d, J=9.2Hz), 7.54(1H, dd, J=8.6, 2.3Hz), 7.39(1H, d, J=2.3Hz), 7.35(1H, d, J=8.6Hz), 6.24(1H, d, J=9.2Hz), 4.93(2H, s), 3.94(3H, s), 1.45(18H, s)

Table 42

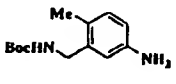
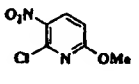
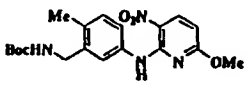
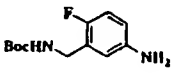
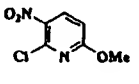
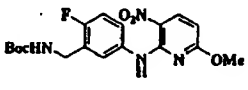
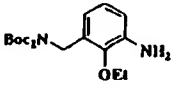
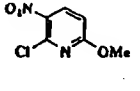
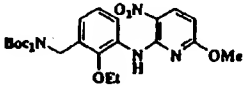
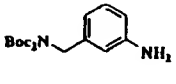
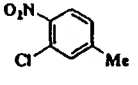
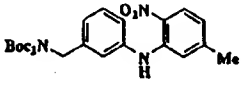
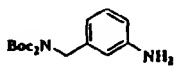
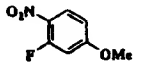
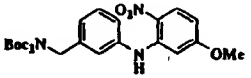
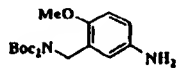
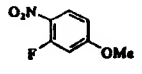
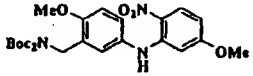
Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
415				base: (1)	^{1}H-NMR($CDCl_3$) δ 10.59(1H, brs), 8.40(1H, d, J=9.2Hz), 7.57 (1H, d, J=2.0Hz), 7.46(1H, dd, J=7.9, 2.0Hz), 7.11(1H, d, J= 7.9Hz), 6.21(1H, d, J=9.2Hz), 4.75(1H, brs), 4.33(2H, d, J= 5.6Hz), 3.96(3H, s), 2.32(3H, s), 1.47(9H, s)
416				base: (1)	^{1}H-NMR($CDCl_3$) δ 10.53(1H, brs), 8.41(1H, d, J=9.2Hz), 7.67 (1H, d, J=8.9Hz), 7.52-7.43(1H, m), 7.05(1H, dd, J=9.2, 8.9 Hz), 6.23(1H, d, J=9.2Hz), 4.92(1H, brs), 4.38(2H, d, J=6.3 Hz), 3.94(3H, s), 1.45(9H, s)
417				base: (1)	^{1}H-NMR($CDCl_3$) δ 11.24(1H, brs), 8.46(1H, d, J=8.9Hz), 8.43 (1H, d, J=7.9Hz), 7.11(1H, dd, J=8.3, 7.9Hz), 6.93(1H, d, J= 8.3Hz), 6.25(1H, d, J=8.9Hz), 4.93(2H, s), 4.04(3H, s), 3.96(2H, q, J=6.9Hz), 1.52(3H, t, J=6.9Hz), 1.45(18H, s)
418				base: (1)	^{1}H-NMR($CDCl_3$) δ 1.47(18H, s), 2.26(3H, s), 4.80(2H, s), 6.59(1H, d, J=8.6Hz), 6.97(1H, s), 7.14-7.21(3H, m), 7.36(1H, dd, J=7.6, 7.6Hz), 8.10(1H, d, J=8.6Hz)

Table 43

Example	Aniline derivative	Halogenated derivative	Product	Reaction condition	Spectral data
419				base : (1)	^{1}H-NMR(CDCl$_3$) δ 1.46(18H, s), 3.74(3H, s), 4.79(2H, s), 6.34(1H, dd, J=9.6, 2.6Hz), 6.57(1H, dd, J=2.6Hz), 7.14-7.20(2H, m), 7.24(1H, s), 7.37(1H, dd, J=7.6, 7.6Hz), 8.18(1H, d, J=9.6Hz), 9.77(1H, brs)
420				base : (2)	^{1}H-NMR(CDCl$_3$) δ 1.44(18H, s), 3.70(3H, s), 3.86(3H, s), 4.81(2H, s), 6.27(1H, dd, J=9.6, 2.6Hz), 6.33(1H, d, J=2.6Hz), 6.89(1H, d, J=8.3Hz), 7.03(1H, d, J=2.0Hz), 7.11(1H, dd, J=8.3, 2.0Hz), 8.16(1H, d, J=9.6Hz), 9.66(1H, s)

Example 2

Synthesis of 2-(3-aminomethylphenylamino)-3-nitropyridine hydrochloride

[0057] A mixture of the compound (95.2 mg) obtained in Example 1 and trifluoroacetic acid (2 ml) was stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting residue was dissolved in methanol (3 ml) and a 1,4-dioxane solution (4 N, 0.5 ml) of hydrogen chloride was added at room temperature and the mixture was concentrated under reduced pressure. In addition, the resulting residue was recrystallized from ethanol-ethyl acetate to give 56.7 mg of the titled compound (yield, 94%)

^{1}H-NMR(DMSO-d_6)
δ:4.03(2H, q, J=5.6Hz), 7.03(1H dd, J=8.2, 4.3Hz), 7.28(1H, d, J=7.6Hz), 7.42(1H, dd, J=7.6, 7.6Hz), 7.74(1H, s), 7.75(1H, d, J=7.6Hz), 8.46(3H, brs), 8.50-8.60(2H, m), 10.00(1H, s)

[0058] The procedure of Example 2 was repeated using corresponding reagents to give the compounds shown in Tables 44 - 62.

Table 44

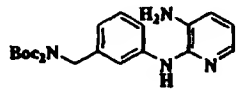
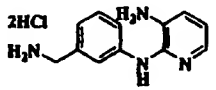
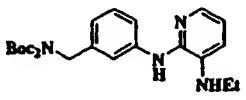
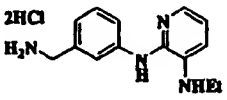
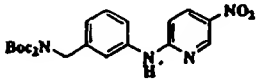
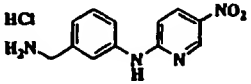
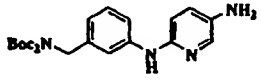
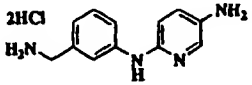
Example	Reagent	Product	Spectral data
4			^{1}H-NMR(DMSO-d_6) δ 3.52(3H, brs), 4.03(2H, q, J=5.6Hz), 6.95(1H, dd, J=7.0, 7.0Hz), 7.28(1H, d, J=7.9Hz), 7.33-7.40(3H, m), 7.48(1H, d, J=7.9Hz), 7.58(1H, s), 8.52(3H, brs), 10.22(1H, brs)
8			^{1}H-NMR(DMSO-d_6) δ 1.30(3H, t, J=6.9Hz), 3.21(2H, q, J=6.9Hz), 4.04(2H, q, J=6.9Hz), 7.01(1H, dd, J=7.9, 5.9Hz), 7.10(1H, d, J=7.3Hz), 7.35(1H, d, J=5.9Hz), 7.39(1H, dd, J=7.3, 7.3Hz), 7.41(1H, d, J=7.3Hz), 7.50(1H, d, J=7.9Hz), 7.59(1H, s), 8.57(3H, brs), 10.55(1H, brs)
10			^{1}H-NMR(DMSO-d_6) δ 4.01(2H, q, J=5.6Hz), 7.08(1H, d, J=9.6Hz), 7.23(1H, d, J=7.6Hz), 7.41(1H, dd, J=7.6, 7.6Hz), 7.74(1H, d, J=7.6Hz), 7.85(1H, s), 8.31(1H, dd, J=9.6, 2.6Hz), 8.47(3H, brs), 9.04(1H, d, J=2.6Hz), 10.52(1H, s)
12			^{1}H-NMR(DMSO-d_6) δ 3.99(2H, q, J=5.3Hz), 7.14(1H, d, J=7.6Hz), 7.14(1H, d, J=8.9Hz), 7.36(1H, dd, J=7.6, 7.6Hz), 7.53(1H, d, J=7.6Hz), 7.67(1H, d, J=8.9Hz), 7.73(1H, s), 8.10(1H, s), 8.49(3H, brs), 9.87(1H, brs)

Table 45

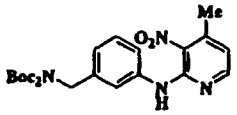
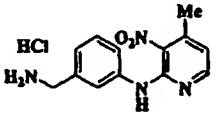
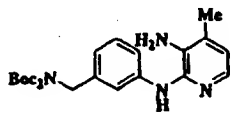
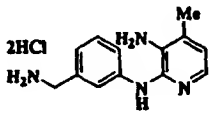
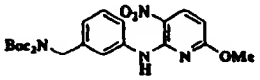
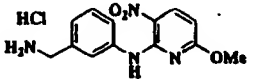
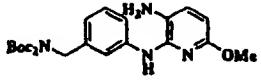
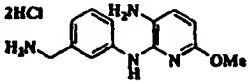
Example	Reagent	Product	Spectral data
14			^{1}H-NMR(DMSO-d_6) δ 2.36(3H, s), 3.97(2H, q, J=5.6Hz), 6.91(1H, d, J=5.0Hz), 7.19(1H, d, J=7.6Hz), 7.34(1H, dd, J=7.6, 7.6Hz), 7.55(1H, d, J=7.6Hz), 7.63(1H, s), 8.20(1H, d, J=5.0Hz), 8.48(3H, brs), 9.08(1H, s)
16			^{1}H-NMR(DMSO-d_6) δ 2.26(3H, s), 3.56(3H, brs), 4.03(2H, q, J=5.6Hz), 6.96(1H, d, J=5.9Hz), 7.30-7.38(3H, m), 7.48(1H, dd, J=7.9, 7.9Hz), 7.53(1H, s), 8.58(3H, brs), 10.23(1H, brs)
18			^{1}H-NMR(DMSO-d_6) δ 3.92(3H, s), 4.03(2H, s), 6.41(1H, d, J=9.2Hz), 7.31(1H, d, J=7.9Hz), 7.45(1H, dd, J=7.9, 7.9Hz), 7.77-7.87(2H, m), 8.46(1H, d, J=9.2Hz), 8.48(3H, brs), 10.49(1H, brs)
20			^{1}H-NMR(DMSO-d_6) δ 3.83(3H, s), 3.98(2H, s), 6.33(1H, d, J=8.6Hz), 7.09(1H, d, J=7.3Hz), 7.36(1H, dd, J=7.3, 7.3Hz), 7.61(1H, d, J=7.3Hz), 7.63(1H, d, J=8.6Hz), 7.76(1H, s)

Table 46

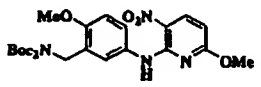
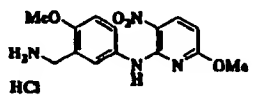
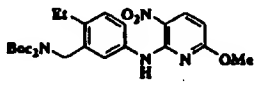
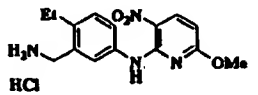
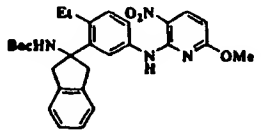
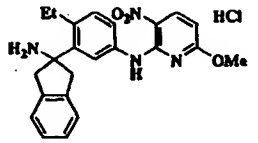
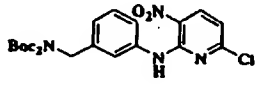
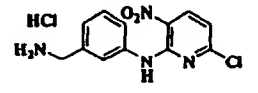
Example	Reagent	Product	Spectral data
22			^{1}H-NMR(DMSO-d_6) δ 3.86(3H, s), 3.89(3H, s), 3.98(2H, s), 6.36(1H, d, J=8.9Hz), 7.12(1H, d, J=8.9Hz), 7.71(1H, s), 7.77(1H, d, J=8.9Hz), 8.31(3H, brs), 8.43(1H, d, J=8.9Hz), 10.42(1H, s)
24			^{1}H-NMR(DMSO-d_6) δ 1.19(3H, t, J=7.6Hz), 2.70(2H, q, J=7.6Hz), 3.94(3H, s), 4.04(2H, s), 6.40(1H, d, J=9.2Hz), 7.31(1H, d, J=8.6Hz), 7.71(1H, d, J=1.3Hz), 7.84(1H, dd, J=8.6, 1.3Hz), 8.40(3H, brs), 8.46(1H, d, J=9.2Hz), 10.50(1H, s)
26			^{1}H-NMR(DMSO-d_6) δ 1.22(3H, t, J=7.3Hz), 2.59(2H, q, J=7.3Hz), 3.63(4H, s), 3.94(3H, s), 6.42(1H, d, J=9.2Hz), 7.29-7.44(5H, m), 7.52(1H, s), 8.05(1H, d, J=8.6Hz), 8.47(1H, d, J=9.2Hz), 8.68(3H, brs), 10.55(1H, s)
28			^{1}H-NMR(DMSO-d_6) δ 4.03(2H, s), 7.05(1H, d, J=8.6Hz), 7.35(1H, d, J=7.6Hz), 7.47(1H, dd, J=7.6, 7.6Hz), 7.62(1H, s), 7.73(1H, d, J=7.6Hz), 8.48(3H, brs), 8.57(1H, d, J=8.6Hz), 10.15(1H, s)

Table 47

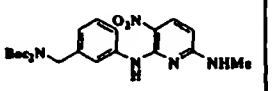
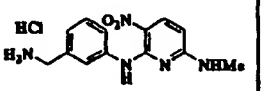
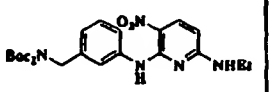
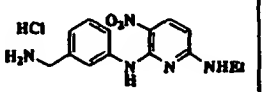
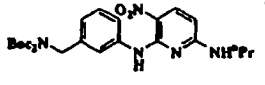
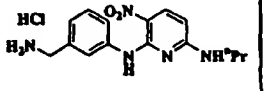
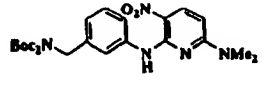
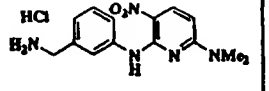
Example	Reagent	Product	Spectral data
30			^{1}H-NMR(DMSO-d_6) δ 2.93(3H, s), 4.04(2H, s), 6.19(1H, d, J=9.2Hz), 7.24(1H, d, J=7.6Hz), 7.44(1H, dd, J=7.6, 7.6Hz), 7.80(1H, s), 7.98(1H, d, J=7.6Hz), 8.10(1H, d, J=9.2Hz)
32			^{1}H-NMR(DMSO-d_6) δ 1.17(3H, t, J=7.3Hz), 3.40(2H, q, J=7.3Hz), 4.01(2H, q, J=5.3Hz), 6.06(1H, brs), 6.19(1H, d, J=9.2Hz), 7.26(1H, d, J=7.3Hz), 7.42(1H, dd, J=7.3, 7.3Hz), 7.77(1H, s), 7.93(1H, d, J=7.3Hz), 8.09(1H, d, J=9.2Hz), 8.52(3H, brs), 10.98(1H, s)
34			^{1}H-NMR(DMSO-d_6) δ 0.92(3H, t, J=7.3Hz), 1.55-1.63(2H, m), 3.29-3.40(2H, m), 4.01(2H, q, J=5.3Hz), 6.10(1H, brs), 6.21(1H, d, J=9.2Hz), 7.27(1H, d, J=7.6Hz), 7.41(1H, dd, J=7.6, 7.6Hz), 7.73(1H, s), 7.97(1H, d, J=7.6Hz), 8.09(1H, d, J=9.2Hz), 8.53(3H, brs), 10.98(1H, s)
36			^{1}H-NMR(DMSO-d_6) δ 3.19(6H, s), 4.01(2H, s), 6.40(1H, d, J=9.6Hz), 7.26(1H, d, J=7.6Hz), 7.42(1H, dd, J=7.6, 7.6Hz), 7.75(1H, s), 7.88(1H, d, J=7.6Hz), 8.21(1H, d, J=9.6Hz), 8.46(3H, brs), 10.78(1H, s)

Table 48

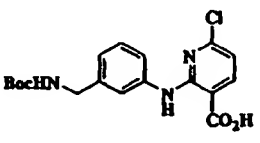
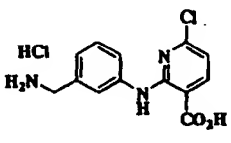
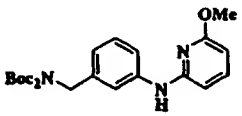
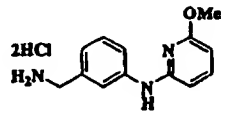
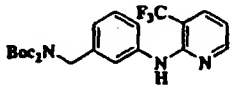
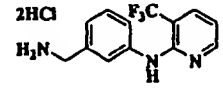
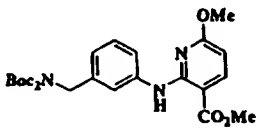
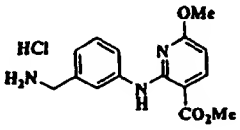
Example	Reagent	Product	Spectral data
38			^{1}H-NMR(DMSO-d_6) δ 4.01(2H, s), 6.93(1H, d, J=8.1Hz), 7.21(1H, d, J=7.6Hz), 7.42(1H, dd, J=7.6, 7.6Hz), 7.55(1H, s), 7.93(1H, d, J=7.6Hz), 8.25(1H, d, J=8.1Hz), 8.46(3H, brs), 10.66(1H, s)
40			^{1}H-NMR(DMSO-d_6) δ 3.88(3H, s), 3.94(2H, q, J=5.6Hz), 6.16(1H, d, J=7.9Hz), 6.49(1H, d, J=7.9Hz), 6.62(2H, brs), 7.05(1H, d, J=7.6Hz), 7.30(1H, dd, J=7.6, 7.6Hz), 7.49(1H, dd, J=7.9, 7.9Hz), 7.63(1H, d, J=7.6Hz), 7.80(1H, s), 8.50(3H, brs)
42			^{1}H-NMR(DMSO-d_6) δ 3.41(2H, s), 6.39(1H, dd, J=7.3, 5.9Hz), 6.68-6.89(4H, m), 7.35(1H, d, J=5.9Hz), 7.67(1H, d, J=7.3Hz)
44			^{1}H-NMR(DMSO-d_6) δ 3.87(3H, s), 3.95(3H, s), 4.01(2H, brs), 6.29(1H, d, J=8.6Hz), 7.15(1H, d, J=7.6Hz), 7.40(1H, dd, J=7.9, 7.6Hz), 7.74(1H, s), 7.88(1H, d, J=7.9Hz), 8.16(1H, d, J=8.6Hz), 8.30(3H, brs), 10.47(1H, s)

Table 49

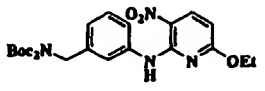
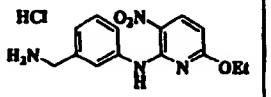
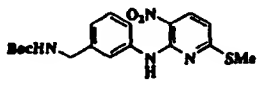
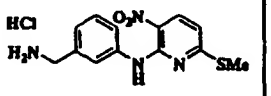
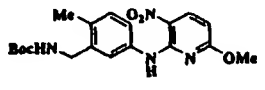
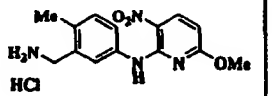
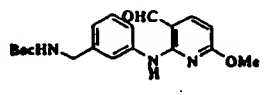
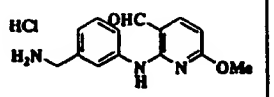
Example	Reagent	Product	Spectral data
57			^{1}H-NMR(DMSO-d_6) δ 1.32(3H, t, J=7.3Hz), 4.03(2H, s), 4.36(2H, q, J=7.3Hz), 6.39(1H, d, J=8.9Hz), 7.31(1H, d, J=7.6Hz), 7.45(1H, dd, J=7.6, 7.6Hz), 7.75(1H, s), 7.79(1H, d, J=7.6Hz), 8.45(1H, d, J=8.9Hz), 8.45(3H, brs), 10.49(1H, s)
61			^{1}H-NMR(DMSO-d_6) δ 3.33(3H, s), 4.03(2H, s), 6.91(1H, d, J=8.9Hz), 7.31(1H, d, J=7.6Hz), 7.45(1H, dd, J=7.6, 7.6Hz), 7.72-7.79(2H, m), 8.34(1H, d, J=8.9Hz), 8.44(3H, brs), 10.33(1H, s)
77			^{1}H-NMR(DMSO-d_6) δ 10.50(1H, brs), 8.45(1H, d, J=9.2Hz), 8.30(3H, brs), 7.78(1H, dd, J=8.3, 2.0Hz), 7.67(1H, d, J=2.0Hz), 7.28(1H, d, J=8.3Hz), 6.38(1H, d, J=9.2Hz), 4.03(2H, s), 3.93(3H, s), 2.37(3H, s)
108			^{1}H-NMR(DMSO-d_6) δ 3.99(3H, s), 4.04(2H, q, J=5.6Hz), 6.40(1H, d, J=8.6Hz), 7.19(1H, d, J=7.9Hz), 7.43(1H, dd, J=7.9, 7.9Hz), 7.74(1H, s), 7.97(1H, d, J=7.9Hz), 8.09(1H, d, J=8.6Hz), 8.27(3H, brs), 9.78(1H, s), 10.96(1H, s)

Table 50

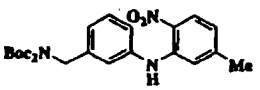
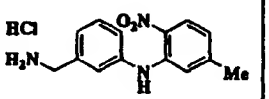
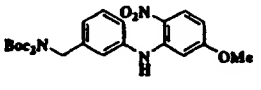
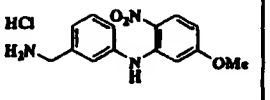
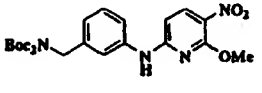
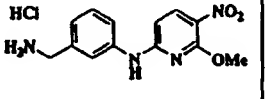
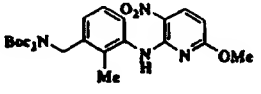
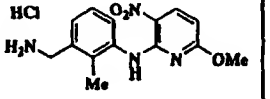
Example	Reagent	Product	Spectral data
151			^{1}H-NMR(DMSO-d_6) δ 2.28(3H, s), 4.03(2H, s), 6.75(1H, d, J=8.9Hz), 7.08(1H, s), 7.27-7.36(2H, m), 7.42-7.49(2H, m), 8.04(1H, d, J=8.9Hz), 8.30(3H, brs), 9.40(1H, s)
153			^{1}H-NMR(DMSO-d_6) δ 3.77(3H, s), 4.05(2H, q, J=4.6Hz), 6.53(1H, dd, J=9.2, 2.3Hz), 6.60(1H, d, J=2.3Hz), 7.34(1H, d, J=7.6Hz), 7.39(1H, d, J=7.6Hz), 7.48(1H, dd, J=7.6, 7.6Hz), 7.54(1H, s), 8.15(1H, d, J=9.2Hz), 8.46(3H, brs), 9.65(1H, s)
457			^{1}H-NMR(DMSO-d_6) δ 10.43(1H, brs), 8.40(3H, brs), 8.28(1H, d, J=8.9Hz), 7.87(1H, s), 7.62-7.54(1H, m), 7.41(1H, dd, J=7.9, 7.6Hz), 7.22(1H, d, J=7.6Hz), 6.61(1H, d, J=8.9Hz), 4.06(3H, s), 4.01(2H, brs) FAB-MS(m/z) 275(M^++1)
458			^{1}H-NMR(DMSO-d_6) δ 10.34(1H, brs), 8.43(1H, d, J=8.9Hz), 8.42-8.20(4H, m), 7.77(1H, dd, J=5.0, 4.6Hz), 7.32(1H, d, J=4.6Hz), 6.33(1H, d, J=8.9Hz), 4.11(2H, s), 3.72(3H, s), 2.29(3H, s) FAB-MS(m/z) 289(M^++1)

Table 51

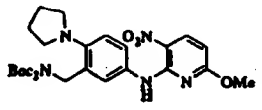
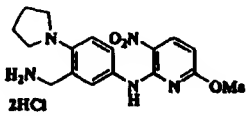
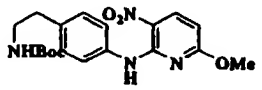
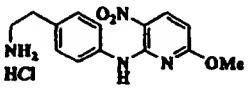
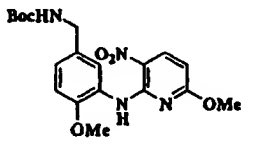
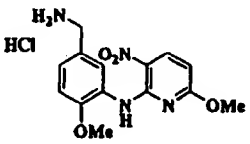
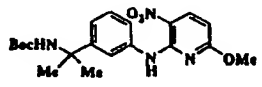
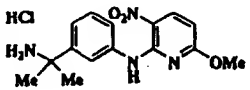
Example	Reagent	Product	Spectral data
459			^{1}H-NMR(DMSO-d_6) δ 10.52(1H, brs), 8.45(1H, d, J=9.2Hz), 8.45-8.28(4H, m), 8.02-7.73(2H, m), 7.40(1H, brs), 6.40(1H, d, J=9.2Hz), 4.23(2H, s), 3.94(3H, s), 3.50-3.20(4H, m), 2.21-1.95(4H, m) FAB-MS(m/z) 344(M^++1)
460			^{1}H-NMR(DMSO-d_6) δ 10.50(1H, s), 8.44(1H, d, J=8.9Hz), 7.98(3H, brs), 7.69(2H, d, J=7.9Hz), 7.28(2H, d, J=7.9Hz), 6.36(1H, d, J=8.9Hz), 3.92(3H, s), 3.15-2.97(2H, m), 2.93(2H, t, J=7.6Hz) FAB-MS(m/z) 289(M^++1)
461			^{1}H-NMR(DMSO-d_6) δ 11.06(1H, s), 8.83(1H, s), 8.46(1H, d, J=8.9Hz), 8.33(3H, brs), 7.57(1H, d, J=7.3Hz), 7.15-7.10(1H, m), 6.38(1H, d, J=8.9Hz), 4.08(2H, s), 3.98(6H, s) FAB-MS(m/z) 305(M^++1)
462			^{1}H-NMR(DMSO-d_6) δ 10.52(1H, s), 8.57(3H, brs), 8.46(1H, d, J=9.2Hz), 7.84(1H, d, J=7.9Hz), 7.75(1H, s), 7.47(1H, dd, J=8.2, 7.9Hz), 7.42-7.35(1H, m), 6.41-6.37(1H, m), 3.91(3H, s), 1.67(6H, s) FAB-MS(m/z) 303(M^++1)

Table 52

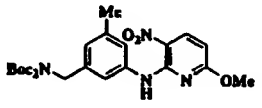
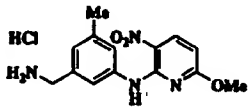
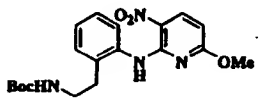
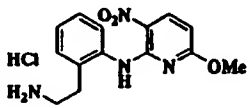
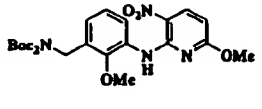
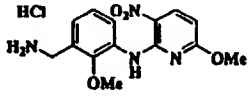
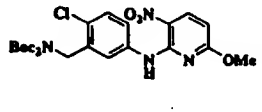
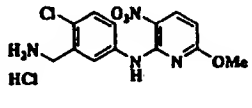
Example	Reagent	Product	Spectral data
463			^{1}H-NMR(DMSO-d_6) δ 10.49(1H, s), 8.45(1H, d, J=8.9Hz), 8.35(3H, brs), 7.68(1H, s), 7.61(1H, s), 7.12(1H, s), 6.40(1H, d, J=8.9Hz), 3.99(2H, s), 3.95(3H, s), 2.36(3H, s) FAB-MS(m/z) 289(M^++1)
464			^{1}H-NMR(DMSO-d_6) δ 10.20(1H, brs), 8.43(1H, d, J=9.2Hz), 7.95(3H, brs), 7.50(1H, dd, J=7.9, 1.7Hz), 7.40-7.25(3H, m), 6.30(1H, d, J=9.2Hz), 3.58(3H, s), 3.03-2.88(4H, m) FAB-MS(m/z) 289(M^++1)
465			^{1}H-NMR(DMSO-d_6) δ 11.09(1H, s), 8.58-8.53(1H, m), 8.51(1H, d, J=9.2Hz), 8.40(3H, brs), 7.32-7.28(2H, m), 6.46(1H, d, J=9.2Hz), 4.11(2H, s), 4.01(3H, s), 3.84(3H, s) FAB-MS(m/z) 305(M^++1)
466			^{1}H-NMR(DMSO-d_6) δ 10.51(1H, brs), 8.50(3H, brs), 8.47(1H, d, J=9.2Hz), 7.93-7.89(2H, m), 7.55(1H, d, J=9.2Hz), 6.43(1H, d, J=9.2Hz), 4.14(2H, s), 3.93(3H, s) FAB-MS(m/z) 309(M^++1)

Table 53

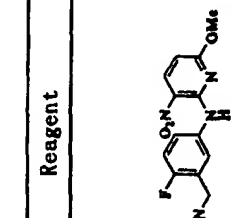
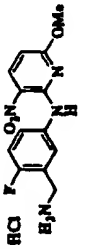
Example	Reagent	Product	Spectral data
467			^{1}H-NMR (DMSO-d_6) δ 10.45 (1H, brs), 8.58-8.37 (4H, m), 7.87-7.79 (2H, m), 7.31 (1H, dd, J=9.2, 8.9Hz), 6.39 (1H, d, J=8.9Hz), 4.07 (2H, s), 3.89 (3H, s)
468			^{1}H-NMR (DMSO-d_6) δ 11.10 (1H, s), 8.57-8.53 (1H, m), 8.50 (1H, d, J=9.2Hz), 8.37 (3H, brs), 7.35-7.24 (2H, m), 6.46 (1H, d, J=9.2Hz), 4.10 (2H, s), 4.01 (3H, s), 3.96 (2H, q, J=6.9Hz), 1.45 (3H, t, J=6.9Hz)
469			^{1}H-NMR (DMSO-d_6) δ 10.85 (1H, brs), 8.50 (1H, d, J=9.2Hz), 8.49 (3H, brs), 8.39 (1H, d, J=7.9Hz), 7.51 (1H, dd, J=7.9, 7.6Hz), 7.42 (1H, d, J=7.6Hz), 6.47 (1H, d, J=9.2Hz), 4.22 (2H, s), 3.90 (3H, s)
470			^{1}H-NMR (DMSO-d_6) δ 9.52 (1H, s), 8.35 (3H, brs), 7.79 (1H, s), 7.70-7.64 (1H, m), 7.35-7.27 (1H, m), 7.06 (1H, d, J=7.6Hz), 6.98 (1H, s), 6.87 (1H, s), 4.02 (2H, s), 3.93 (3H, s), 3.87 (3H, s)

Table 54

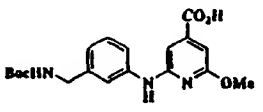
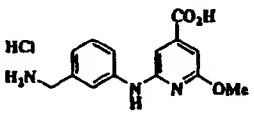
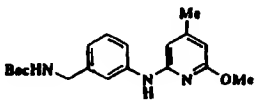
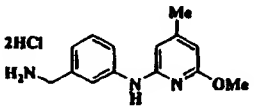
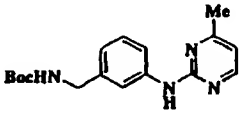
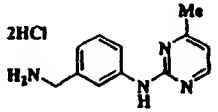
Example	Reagent	Product	Spectral data
471			^{1}H-NMR(DMSO-d_6) δ 13.28(1H, brs), 9.47(1H, s), 8.34(3H, brs), 7.79(1H, s), 7.65(1H, d, J=8.6Hz), 7.33(1H, dd, J=8.6, 7.3Hz), 7.06(1H, d, J=7.3Hz), 6.96(1H, s), 6.53(1H, s), 3.97(2H, d, J=5.3Hz), 3.92(3H, s)
473			^{1}H-NMR(D_2O) δ 7.63-7.52(1H, m), 7.45-7.37(3H, m), 6.54(1H, s), 6.41(1H, s), 4.22(2H, s), 4.02(3H, s), 2.37(3H, s)
474			^{1}H-NMR(DMSO-d_6) δ 9.89(1H, brs), 8.43(3H, brs), 8.38(1H, d, J=5.3Hz), 7.83(1H, s), 7.73(1H, d, J=7.9Hz), 7.34(1H, dd, J=7.9, 7.6Hz), 7.13(1H, d, J=7.6Hz), 6.82(1H, d, J=5.3Hz), 3.97(2H, q, J=5.6Hz), 2.41(3H, s)

Table 55

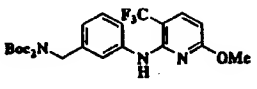
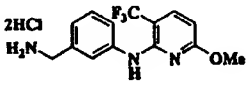
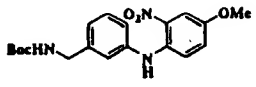
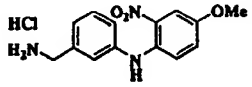
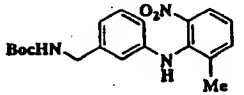
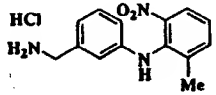
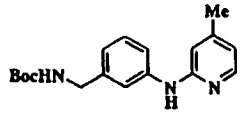
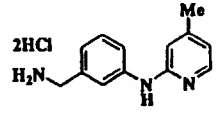
Example	Reagent	Product	Spectral data
475			^{1}H-NMR(DMSO-d_6) δ 3.78(3H, s), 3.98(2H, s), 6.33(1H, d, J=8.2Hz), 7.18(1H, d, J=7.6Hz), 7.35(1H, dd, J=7.6, 7.6Hz), 7.57(1H, d, J=7.6Hz), 7.69(1H, s), 7.84(1H, d, J=8.2Hz), 8.16(1H, s), 8.37(3H, brs)
476			^{1}H-NMR(DMSO-d_6) δ 3.81(3H, s), 3.98(2H, s), 7.17(1H, d, J=7.6Hz), 7.21(1H, d, J=7.6Hz), 7.25(1H, dd, J=9.2, 3.0Hz), 7.32(1H, s), 7.38(1H, dd, J=7.6, 7.6Hz), 7.39(1H, d, J=9.2Hz), 7.57(1H, d, J=3.0Hz), 8.36(3H, brs), 9.02(1H, s)
477			^{1}H-NMR(DMSO-d_6) δ 2.18(3H, s), 3.87(2H, s), 6.58(1H, d, J=7.9Hz), 6.63(1H, s), 6.87(1H, d, J=7.6Hz), 7.18(1H, dd, J=7.6, 7.6Hz), 7.32(1H, dd, J=7.9, 7.9Hz), 7.62(1H, d, J=7.6Hz), 7.80(1H, d, J=7.9Hz), 8.12(1H, s), 8.28(3H, brs)
478			^{1}H-NMR(DMSO-d_6) δ 2.40(3H, s), 4.05(2H, q, J=5.3Hz), 6.93(1H, d, J=6.3Hz), 7.14(1H, s), 7.34-7.39(2H, m), 7.49(1H, dd, J=7.6, 7.6Hz), 7.62(1H, s), 8.02(1H, d, J=6.3Hz), 8.59(3H, brs), 10.83(1H, brs)

Table 56

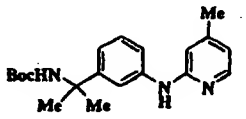
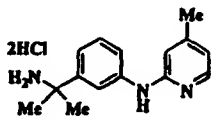
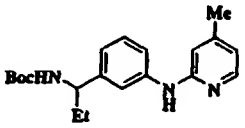
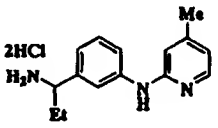
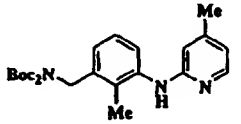
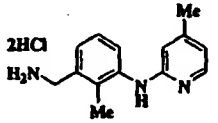
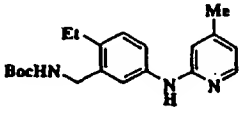
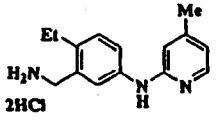
Example	Reagent	Product	Spectral data
479			^{1}H-NMR (DMSO-d_6) δ 1.66 (6H, s), 2.38 (3H, s), 6.90 (1H, d, J=6.3Hz), 7.04 (1H, s), 7.40-7.53 (3H, m), 7.62 (1H, s), 8.00 (1H, d, J=6.3Hz), 8.76 (3H, brs), 10.52 (1H, brs)
480			^{1}H-NMR (DMSO-d_6) δ 0.81 (3H, t, J=7.3Hz), 1.83-2.06 (2H, m), 2.39 (3H, s), 4.10-4.25 (1H, m), 6.92 (1H, d, J=6.3Hz), 7.11 (1H, s), 7.37 (1H, d, J=7.6Hz), 7.39 (1H, d, J=7.6Hz), 7.50 (1H, dd, J=7.6, 7.6Hz), 7.60 (1H, s), 8.02 (1H, d, J=6.3Hz), 8.69 (3H, brs), 10.76 (1H, brs)
481			^{1}H-NMR (DMSO-d_6) δ 2.26 (3H, s), 2.38 (3H, s), 4.11 (2H, q, J=5.3Hz), 6.87 (1H, d, J=6.9Hz), 6.87 (1H, s), 7.33-7.52 (3H, m), 7.92 (1H, d, J=6.9Hz), 8.58 (3H, brs), 10.67 (1H, brs)
482			^{1}H-NMR (DMSO-d_6) δ 1.20 (3H, t, J=7.6Hz), 2.41 (3H, s), 2.72 (2H, q, J=7.6Hz), 4.07 (2H, q, J=5.6Hz), 6.92 (1H, d, J=6.3Hz), 7.12 (1H, s), 7.30 (1H, d, J=8.3Hz), 7.35 (1H, d, J=8.3Hz), 7.57 (1H, s), 8.00 (1H, d, J=6.3Hz), 8.61 (3H, brs), 10.79 (1H, brs)

Table 57

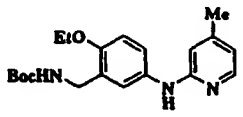
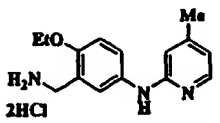
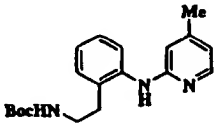
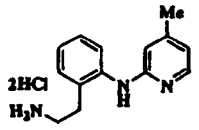
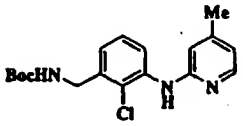
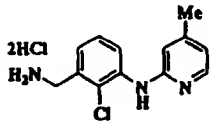
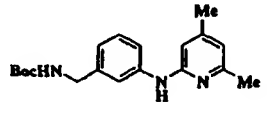
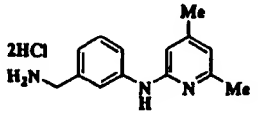
Example	Reagent	Product	Spectral data
483			^{1}H-NMR(DMSO-d_6) δ 1.40(3H, t, J=6.9Hz), 2.38(3H, s), 3.99(2H, q, J=5.3Hz), 4.13(2H, q, J=6.9Hz), 6.87(1H, d, J=6.3Hz), 7.03(1H, s), 7.15(1H, d, J=8.9Hz), 7.33(1H, dd, J=8.9, 1.7Hz), 7.51(1H, d, J=1.7Hz), 7.94(1H, d, J=6.3Hz), 8.48(3H, brs), 10.72(1H, brs)
484			^{1}H-NMR(DMSO-d_6) δ 2.37(3H, s), 2.88-3.10(4H, m), 6.88(1H, d, J=6.6Hz), 6.95(1H, s), 7.39-7.50(4H, m), 7.89(1H, d, J=6.6Hz), 8.12(3H, brs), 10.69(1H, brs)
485			^{1}H-NMR(DMSO-d_6) δ 2.39(3H, s), 4.19(2H, q, J=5.0Hz), 6.93(1H, d, J=6.3Hz), 6.98(1H, s), 7.48-7.68(3H, m), 7.97(1H, d, J=6.3Hz), 8.71(3H, brs), 10.56(1H, brs)
486			^{1}H-NMR(DMSO-d_6) δ 2.35(3H, s), 2.49(3H, s), 4.05(2H, q, J=5.3Hz), 6.82(1H, s), 7.00(1H, s), 7.33-7.38(2H, m), 7.48(1H, dd, J=7.6, 7.6Hz), 7.56(1H, s), 8.58(3H, brs), 10.30(1H, brs)

Table 58

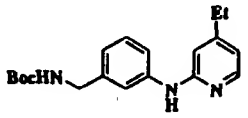
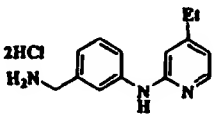
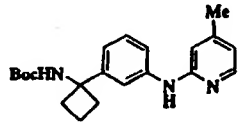
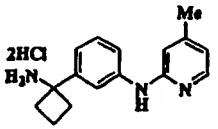
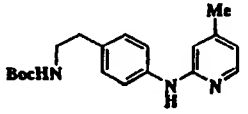
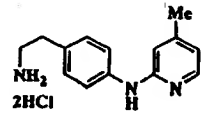
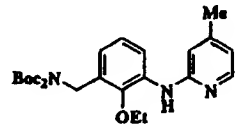
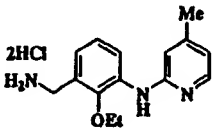
Example	Reagent	Product	Spectral data
487			^{1}H-NMR(DMSO-d_6) δ 1.20(3H, t, J=7.3Hz), 2.71(2H, q, J=7.3Hz), 4.05(2H, q, J=5.3Hz), 6.98(1H, d, J=6.3Hz), 7.18(1H, s), 7.34-7.42(2H, m), 7.49(1H, dd, J=7.6, 7.6Hz), 7.64(1H, s), 8.03(1H, d, J=6.3Hz), 8.66(3H, brs), 11.00(1H, brs)
488			^{1}H-NMR(DMSO-d_6) δ 1.73-1.85(1H, m), 2.15-2.27(1H, m), 2.40(3H, s), 2.56-2.66(4H, m), 6.92(1H, d, J=6.3Hz), 7.13(1H, s), 7.35-7.42(2H, m), 7.53(1H, dd, J=7.6, 7.6Hz), 7.63(1H, s), 8.00(1H, d, J=6.3Hz), 8.94(3H, brs), 10.84(1H, brs)
489			^{1}H-NMR(DMSO-d_6) δ 2.37(3H, s), 2.87-3.15(4H, m), 6.87(1H, d, J=6.3Hz), 7.01(1H, s), 7.37(4H, s), 7.92(1H, d, J=6.3Hz), 8.16(3H, brs), 10.65(1H, brs)
490			^{1}H-NMR(DMSO-d_6) δ 1.13(3H, t, J=6.9Hz), 2.40(3H, s), 3.86(2H, q, J=6.9Hz), 4.06(2H, q, J=5.3Hz), 6.93(1H, d, J=5.9Hz), 7.07(1H, s), 7.28(1H, dd, J=7.6, 7.6Hz), 7.45(1H, d, J=7.6Hz), 7.51(1H, d, J=7.6Hz), 7.96(1H, d, J=5.9Hz), 8.54(3H, brs), 10.71(1H, brs)

Table 59

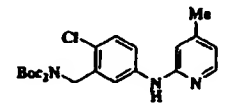
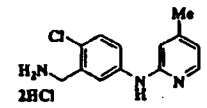
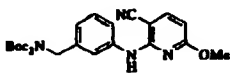
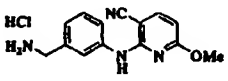
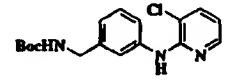
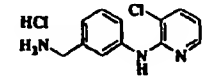
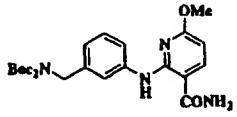
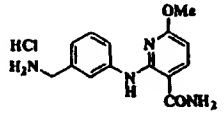
Example	Reagent	Product	Spectral data
491			^{1}H-NMR (DMSO-d_6) δ 2.41 (3H, s), 4.14 (2H, q, J=5.3Hz), 6.95 (1H, d, J=6.3Hz), 7.18 (1H, s), 7.44 (1H, dd, J=8.6, 2.0Hz), 7.58 (1H, d, J=8.6Hz), 7.79 (1H, d, J=2.0Hz), 8.04 (1H, d, J=6.3Hz), 8.76 (3H, brs), 10.89 (1H, brs)
492			^{1}H-NMR (DMSO-d_6) δ 3.86 (3H, s), 4.01 (2H, q, J=5.9Hz), 6.36 (1H, d, J=8.5Hz), 7.19 (1H, d, J=7.8Hz), 7.38 (1H, dd, J=7.8, 7.8Hz), 7.63 (1H, d, J=7.8Hz), 7.77 (1H, s), 7.95 (1H, d, J=8.5Hz), 8.41 (3H, brs), 9.28 (1H, s)
493			^{1}H-NMR (DMSO-d_6) δ 3.98 (2H, q, J=5.3Hz), 6.86 (1H, dd, J=7.9, 5.0Hz), 7.14 (1H, d, J=7.6Hz), 7.34 (1H, dd, J=7.6, 7.6Hz), 7.66 (1H, d, J=7.6Hz), 7.76-7.86 (2H, m), 8.10 (1H, dd, J=5.0, 1.3Hz), 8.38 (3H, brs), 8.47 (1H, s)
494			^{1}H-NMR (DMSO-d_6) δ 3.93 (3H, s), 4.01 (2H, q, J=5.9Hz), 6.24 (1H, d, J=8.6Hz), 7.08 (1H, d, J=7.9Hz), 7.37 (1H, dd, J=7.9, 7.9Hz), 7.42 (1H, brs), 7.65 (1H, s), 7.88 (1H, d, J=7.9Hz), 8.04 (1H, brs), 8.14 (1H, d, J=8.6Hz), 8.22 (3H, brs), 11.76 (1H, s)

Table 60

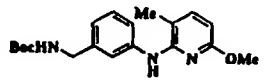
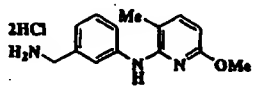
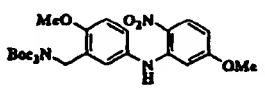
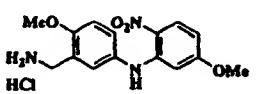
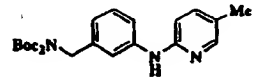
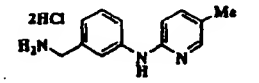
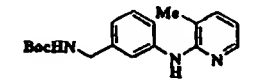
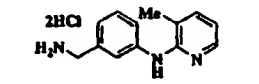
Example	Reagent	Product	Spectral data
495			^{1}H-NMR(DMSO-d_6) δ 2.19(3H, s), 3.79(3H, s), 3.94(2H, q, J=5.6Hz), 6.16(1H, d, J=7.6Hz), 7.03(1H, d, J=7.9Hz), 7.29(1H, dd, J=7.9, 7.9Hz), 7.36(1H, d, J=7.6Hz), 7.64(1H, d, J=7.9Hz), 7.82(1H, s), 7.95(1H, brs), 8.35(3H, brs)
496			^{1}H-NMR(DMSO-d_6) δ 3.74(3H, s), 3.88(3H, s), 4.00(2H, q, J=5.3Hz), 6.35(1H, d, J=2.3Hz), 6.46(1H, dd, J=9.6, 2.3Hz), 7.15(1H, d, J=8.6Hz), 7.40(1H, d, J=8.6Hz), 7.43(1H, s), 8.13(1H, d, J=9.6Hz), 8.18(3H, brs), 9.60(1H, s)
501			^{1}H-NMR(DMSO-d_6) δ 2.25(3H, s), 4.21(2H, q, J=5.6Hz), 7.26-7.50(4H, m), 7.62(1H, s), 7.88(1H, d, J=10.2Hz), 7.95(1H, s), 8.57(3H, brs), 10.77(1H, brs)
502			^{1}H-NMR(DMSO-d_6) δ 2.40(3H, s), 4.04(2H, q, J=5.6Hz), 7.42(1H, dd, J=6.6, 6.6Hz), 7.40-7.57(3H, m), 7.66(1H, s), 7.90-7.99(2H, m), 8.65(3H, brs), 9.77(1H, brs)

Table 61

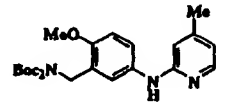
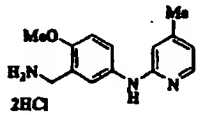
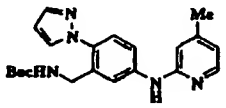
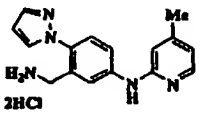
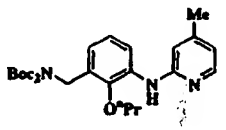
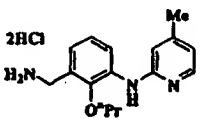
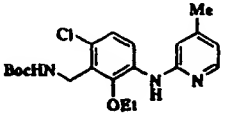
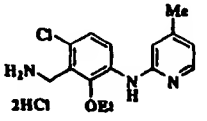
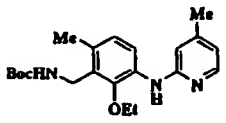
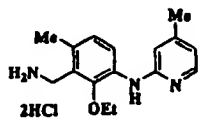
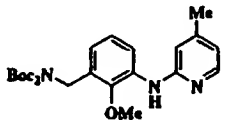
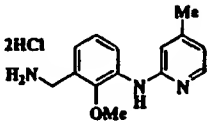
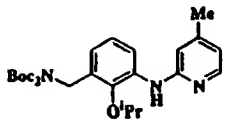
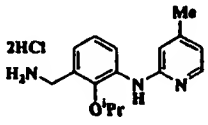
Example	Reagent	Product	Spectral data
503			^{1}H-NMR(CDCl$_3$) δ 2.38(3H, s), 3.88(3H, s), 3.99(2H, q, J=5.6Hz), 6.87(1H, d, J=6.3Hz), 7.02(1H, s), 7.17(1H, d, J=8.6Hz), 7.36(1H, dd, J=8.6, 2.0Hz), 7.51(1H, d, J=2.0Hz), 7.94(1H, d, J=6.3Hz), 8.46(3H, brs), 10.70(1H, brs)
504			^{1}H-NMR(CDCl$_3$) δ 2.43(3H, s), 3.99(2H, q, J=5.3Hz), 6.61(1H, s), 6.97(1H, d, J=5.9Hz), 7.23(1H, s), 7.53-7.64(2H, m), 7.83(1H, s), 7.88(1H, s), 8.07(1H, d, J=5.9Hz), 8.24-8.28(1H, m), 8.66(3H, brs), 11.01(1H, brs)
506			^{1}H-NMR(DMSO-d6) δ 8.46(3H, brs), 7.95(1H, d, J=6.3Hz), 7.55-7.36(2H, m), 7.28(1H, dd, J=7.9, 7.6Hz), 7.01(1H, s), 6.91(1H, d, J=6.3Hz), 4.06(2H, q, J=5.3Hz), 3.75(2H, t, J=6.6HZ), 2.40(3H, s), 1.60-1.51(2H, m), 0.76(3H, t, J=7.3Hz)
521			^{1}H-NMR(DMSO-d6) δ 1.13(3H, t, J=6.9Hz), 2.42(3H, s), 3.91(2H, q, J=6.9Hz), 4.16(2H, q, J=5.0Hz), 6.95(1H, d, J=6.3Hz), 7.13(1H, s), 7.42(1H, d, J=8.6Hz), 7.51(1H, d, J=8.6Hz), 7.95(1H, d, J=6.3Hz), 8.54(3H, brs), 10.96(1H, brs)

Table 62

Example	Reagent	Product	Spectral data
522			^{1}H-NMR(DMSO-d_6) δ 1.10(3H, t, J=6.9Hz), 2.41(3H, s), 2.46(3H, s), 3.84(2H, q, J=6.9Hz), 3.96-4.19(2H, m), 6.91(1H, d, J=6.3Hz), 7.04-7.19(2H, m), 7.30(1H, d, J=7.9Hz), 7.94(1H, d, J=6.3Hz), 8.47(3H, brs), 10.95(1H, brs)
541			^{1}H-NMR(DMSO-d_6) δ 10.68(1H, brs), 8.46(3H, brs), 7.94(1H, d, J=5.9Hz), 7.55-7.36(2H, m), 7.32-7.22(1H, m), 7.06(1H, s), 6.90(1H, d, J=5.9Hz), 4.06(2H, s), 3.67(3H, s), 2.40(3H, s)
543			^{1}H-NMR(DMSO-d_6) δ 10.66(1H, brs), 8.48(3H, brs), 7.95(1H, d, J=6.3Hz), 7.50(1H, d, J=8.3Hz), 7.44(1H, d, J=7.6Hz), 7.27(1H, dd, J=8.3, 7.6Hz), 7.06(1H, s), 6.92(1H, d, J=6.3Hz), 4.27-4.12(1H, m), 4.07(2H, q, J=5.3Hz), 2.41(3H, s), 1.07(6H, d, J=5.9Hz)

Example 3

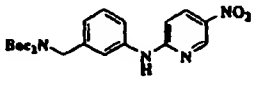
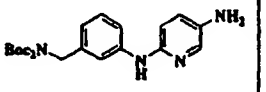
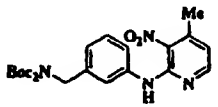
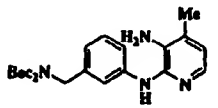
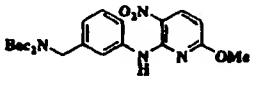
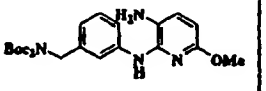
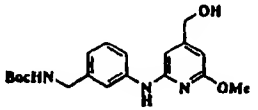
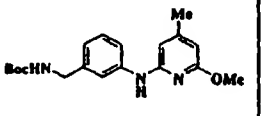
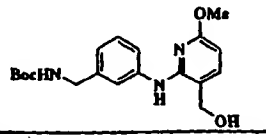
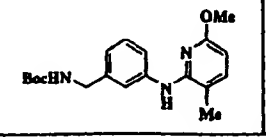
Synthesis of 3-amino-2-(3-(di(t-butoxycarbonyl)aminomethyl)phenyl-amino)pyridine

[0059] A mixture of the compound (1.41 g) obtained in Example 1, 10% palladium-carbon (170 mg), methanol (60 ml) and ethyl acetate (30 ml) was stirred in a hydrogen atmosphere at room temperature for one day. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 1.15 g of the titled compound (yield, 88%).

^{1}H-NMR ($CDCl_3$)
δ:1.45(18H, s), 3.40(2H, brs), 4.75(2H, s), 6.20(1H, brs), 6.77(1H, dd, J=7.6, 5.0Hz), 6.84-6.90(1H, m), 7.00(1H, dd, J=7.6, 1.3Hz), 7.13(1H, s), 7.19-7.23(2H, m), 7.82 (1H, dd, J=5.0, 1.3Hz)

[0060] The procedure of Example 3 was repeated using corresponding reagents to give the compounds shown in Table 63.

Table 63

Example	Reagent	Product	Spectral data
11			^{1}H-NMR(CDCl$_3$) δ 1.45(18H, s), 3.38(2H, brs), 4.74(2H, s), 6.35(1H, brs), 6.83(1H, d, J=8.9Hz), 6.86(1H, d, J=7.6Hz), 6.98(1H, dd, J=8.9, 2.6Hz), 7.10(1H, s), 7.12(1H, d, J=7.6Hz), 7.20(1H, dd, J=7.6, 7.6Hz), 7.79(1H, d, J=2.6Hz)
15			^{1}H-NMR(CDCl$_3$) δ 1.44(18H, s), 2.22(3H, s), 3.41(2H, brs), 4.73(2H, s), 6.11(1H, brs), 6.72(1H, d, J=5.0Hz), 6.85(1H, d, J=7.6Hz), 7.01(1H, s), 7.07(1H, d, J=7.6Hz), 7.20(1H, dd, J=7.6, 7.6Hz), 7.72(1H, d, J=5.0Hz)
19			^{1}H-NMR(CDCl$_3$) δ 1.44(18H, s), 3.88(3H, s), 4.76(2H, s), 6.15(1H, d, J=8.3Hz), 6.74(1H, brs), 6.86(1H, d, J=7.8Hz), 7.06(1H, d, J=8.3Hz), 7.23(1H, dd, J=7.8, 7.8Hz), 7.36(1H, s), 7.49(1H, d, J=7.8Hz)
445			^{1}H-NMR(CDCl$_3$) δ 7.35(1H, s), 7.30-7.23(2H, m), 6.92-6.87(1H, m), 6.31(1H, brs), 6.21(1H, s), 6.05(1H, s), 4.81(1H, brs), 4.30(2H, d, J=5.6Hz), 3.89(3H, s), 2.22(3H, s), 1.46(9H, s)
455			^{1}H-NMR(CDCl$_3$) δ 1.46(9H, s), 2.17(3H, s), 3.91(3H, s), 4.31(2H, d, J=5.6Hz), 4.80(1H, brt), 6.13(1H, s), 6.18(1H, d, J=7.9Hz), 6.89(1H, d, J=7.3Hz), 7.21-7.30(2H, m), 7.49(1H, d, J=7.3Hz), 7.62(1H, s)

Example 5

Synthesis of 3-methylamino-2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)pyridine

[0061] To a mixture of the compound (88.5 mg) obtained in Example 3, methyl iodide (15 µl) and dimethylformamide (2 ml), sodium hydride (content = 60%; 10 mg) was added and the resulting mixture was stirred at room temperature for 4 days. To the reaction mixture, ethyl acetate and a saturated aqueous sodium hydrogencarbonate solution were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 3) to give 19.3 mg of the titled compound (yield, 21%).

^{1}H-NMR ($CDCl_3$)
δ:1.44(18H, s), 2.85(3H, s), 3.48(1H, brs), 4.74(2H, s), 6.02(1H, s), 6.82-6.95(3H, m), 7.03(1H, s), 7.09(1H, d, J=8.0Hz), 7.20(1H, dd, J=8.0, 8.0Hz), 7.75 (1H, dd, J=4.3, 1.7Hz)

Example 6

Synthesis of 3-methylamino-2-(3-aminomethylphenylamino)pyridine

[0062] Using the compound obtained in Example 5 as a starting material, reaction was performed as in Example 2 and thereafter the liquid reaction mixture was concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, chloroform: methanol = 10 : 1) to give the titled compound quantitatively.

^{1}H-NMR ($CDCl_3$)
δ:1.69(2H, brs), 2.85(3H, s), 3.53(1H, brs), 3.81(2H, s), 6.08(1H, brs), 6.84-6.94(3H, m), 7.05(1H, d, J=7.6Hz), 7.12(1H, s), 7.22(1H, dd, J=7.6, 7.6Hz), 7.76 (1H, dd, J=4.6, 2.0Hz)

Example 7

Synthesis of 3-ethylamino-2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)pyridine

[0063] Using the compound obtained in Example 3 as a starting material and also using ethyl iodide as a reagent, the procedure of Example 5 was repeated to give the titled compound (yield, 54%).

^{1}H-NMR ($CDCl_3$)
δ:1.28(3H, t, J=7.3Hz), 1.45(18H, s), 3.15(2H, q, J=7.3Hz), 3.30(1H, brs), 4.74(2H, s), 6.05(1H, s), 6.82-6.96(3H, m), 7.07(1H, s), 7.12-7.18(1H, m), 7.18 (1H, dd, J=7.3, 7.3Hz), 7.75(1H, dd, J=4.6, 1.3Hz)

Example 29

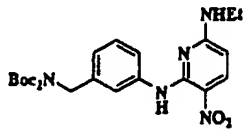
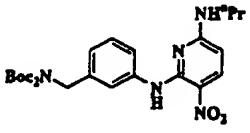
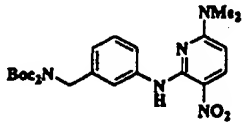
Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-6-methylamino-3-nitropyridine

[0064] A mixture of the compound (77.0 mg) obtained in Example 27, potassium carbonate (89 mg), methylamine hydrochloride (22.0 mg) and acetonitrile (2 ml) was stirred at 60°C for 6 h and the reaction mixture was concentrated under reduced pressure. Ethyl acetate and water were added to the resulting residue. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 71.0 mg of the titled compound (yield, 93%).

^{1}H-NMR ($CDCl_3$)
δ:1.43(18H, s), 3.03(3H, d, J=4.3Hz), 4.81(2H, s), 5.93(1H, d, J=8.9Hz), 6.98-7.80(5H, m), 8.20-8.42(1H, m), 10.81(1H, brs)

[0065] The procedure of Example 29 was repeated using corresponding amine derivatives to give the compounds shown in Table 64.

Table 64

Example	Amine derivative	Product	Spectral data
3 1	$NH_2Et.HCl$		^1H-NMR($CDCl_3$) δ 1.32(3H, t, J=6.9Hz), 1.43(18H, s), 3.38-3.52(2H, m), 4.81(2H, s), 5.92(1H, d, J=9.2Hz), 6.97-7.78(5H, m), 8.26(1H, d, J=9.2Hz), 10.79(1H, brs)
3 3	$NH_2{}^nPr.HCl$		^1H-NMR($CDCl_3$) δ 1.00(3H, t, J=7.3Hz), 1.43(18H, s), 1.62-1.80(2H, m), 3.22-3.44(2H, m), 4.81(2H, s), 5.93(1H, d, J=6.5Hz), 6.95-7.83(5H, m), 8.20-8.37(1H, m), 10.80(1H, brs)
3 5	$NHMe_2.HCl$		^1H-NMR($CDCl_3$) δ 1.46(18H, s), 3.19(6H, s), 4.78(2H, s), 6.08(1H, d, J=9.6Hz), 7.04(1H, d, J=7.6Hz), 7.29(1H, dd, J=7.6, 7.6Hz), 7.58(1H, s), 7.59(1H, d, J=7.6Hz), 8.28(1H, d, J=9.6Hz), 10.81(1H, brs)

Example 37

Synthesis of 6-chloro-2-(3-(t-butoxycarbonylaminomethyl)phenylamino)nicotinic acid

[0066] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (81 mg), 2,6-dichloronicotinic acid (90%, 53 mg), di-i-propylethylamine (64 mg) and 1,4-dioxane (1 ml) was heated under reflux for 3 days and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, methylene chloride:methanol = 20 : 1) to give 24 mg of the titled compound (yield, 25%).

^1H-NMR (DMSO-d_6)
δ:1.44(9H, s), 4.14-4.26(2H, m), 6.72(1H, d, J=7.9Hz), 6.89(1H, d, J=7.6Hz), 7.09(1H, brt), 7.26(1H, dd, J=7.6, 7.6Hz), 7.51(1H, s), 7.71 (1H, d, J=7.6Hz), 8.22(1H, d, J=7.9Hz)

Example 39

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-6-methoxypyridine

[0067] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (50 mg), tetrakistriphenylphosphine palla mg), potassium carbonate (24 mg), 2-chloro-6-methoxypyridine (25 mg) and toluene (3 ml) was heated ne under nitrogen atmosphere for 16 h and, thereafter, ethyl acetate and water were added. The organic laye with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and con reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, et

= 1 : 4) to give 54.5 mg of the titled compound (yield, 82%).

^{1}H-NMR ($CDCl_3$)
δ:1.45(18H, s), 3.91(3H, s), 4.77(2H, s), 6.19(1H, d, J=7.9Hz), 6.36(1H, brs), 6.39(1H, d, J=7.9Hz), 6.93(1H, d, J=6.9Hz) 7.23-7.30(3H, m), 7.39(1H, dd, J=7.9, 7.9Hz)

[0068] The procedure of Example 39 was repeated using corresponding aniline derivatives and corresponding halogenated derivatives to give the compounds shown in Tables 65 - 73 (under "Reaction conditions" in the tables: palladium Pd:(1) is tetrakistriphenylphosphine palladium, Pd:(2) is tris(dibenzylideneacetone)dipalladium, base:(1) is potassium t-butoxide, base:(2) is sodium t-butoxide, base:(3) is potassium carbonate; ligand:(1) is diphenylphosphinoferrocene and ligand:(2) is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

Table 65

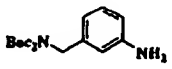
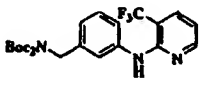
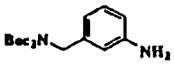
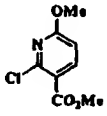
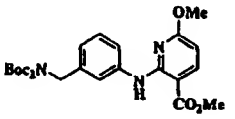
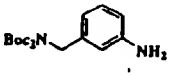
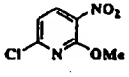
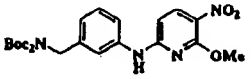
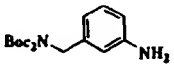
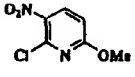
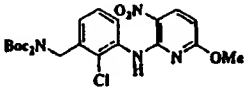
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
41				Pd : (1) base : (3)	^{1}H-NMR δ ($CDCl_3$) 1.47(18H, s), 4.78(2H, s), 6.71(1H, brs), 6.81(1H, dd, J=7.6, 4.3Hz), 7.02(1H, d, J=7.6Hz), 7.29(1H, dd, J=7.6, 7.6Hz), 7.43(1H, s), 7.49(1H, d, J=7.6Hz), 7.79(1H, d, J=7.6Hz), 8.33(1H, d, J=4.3Hz)
43				Pd : (1) base : (3)	^{1}H-NMR($CDCl_3$) δ 1.45(18H, s), 3.88(3H, s), 3.97(3H, s), 4.78(2H, s), 6.14(1H, d, J=8.8Hz), 6.95(1H, d, J=7.6Hz), 7.26(1H, dd, J=7.6, 7.6Hz), 7.59(1H, d, J=7.6Hz), 7.66(1H, s), 8.10(1H, d, J=8.8Hz), 10.42(1H, brs)
421				Pd : (1) base : (3)	^{1}H-NMR($CDCl_3$) δ 8.27(1H, d, J=8.9Hz), 7.45-7.30(3H, m), 7.16-7.06(2H, m), 6.32(1H, d, J=8.9Hz), 4.79(2H, s), 4.09(3H, s), 1.46(18H, s)
422				Pd : (1) base : (3)	^{1}H-NMR($CDCl_3$) δ 11.00(1H, brs), 8.46(1H, d, J=9.2Hz), 8.28(1H, d, J=8.3Hz), 7.28(1H, dd, J=8.3, 7.9Hz), 6.99(1H, d, J=7.9Hz), 6.28(1H, d, J=9.2Hz), 4.95(2H, s), 3.95(3H, s), 1.46(18H, s)

Table 66

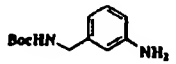
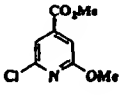
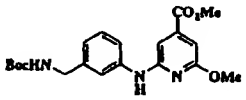
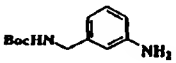
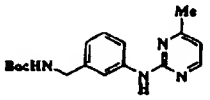
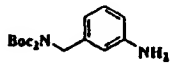
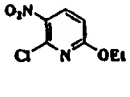
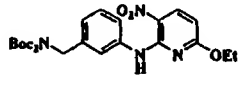
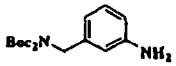
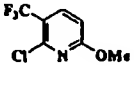
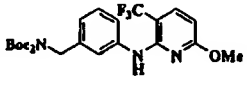
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
423				Pd : (2) base : (2) ligand : (2)	^{1}H-NMR($CDCl_3$) δ 7.38(1H, brs), 7.34-7.27(2H, m), 6.96(1H, d, J=6.6Hz), 6.89(1H, s), 6.74(1H, s), 6.51(1H, s), 4.83(1H, brs), 4.31(2H, d, J=5.6Hz), 3.94(3H, s), 3.90(3H, s), 1.46(9H, s)
424				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 8.27(1H, d, J=5.6Hz), 7.58(1H, s), 7.55(1H, d, J=7.9Hz), 7.28(1H, dd, J=7.9, 7.3Hz), 7.10(1H, brs), 6.94(1H, d, J=7.3Hz), 6.61(1H, d, J=5.6Hz), 4.83(1H, brs), 4.32(2H, d, J=5.6Hz), 2.42(3H, s), 1.47(9H, s)
425				Pd : (1) base : (3)	^{1}H-NMR($CDCl_3$) δ 1.39(3H, t, J=6.9Hz), 1.47(18H, s), 4.39(2H, q, J=6.9Hz), 4.79(2H, s), 6.20(1H, d, J=8.9Hz), 7.11(1H, d, J=7.6Hz), 7.32(1H, dd, J=7.6, 7.6Hz), 7.53(1H, s), 7.57(1H, d, J=7.6Hz), 8.41(1H, d, J=8.9Hz), 10.61(1H, brs)
426				Pd : (1) base : (3)	^{1}H-NMR($CDCl_3$) δ 1.46(18H, s), 3.90(3H, s), 4.77(2H, s), 6.22(1H, d, J=8.6Hz), 6.73(1H, brs), 6.99(1H, d, J=7.6Hz), 7.26(1H, dd, J=7.6, 7.6Hz), 7.44(1H, s), 7.49(1H, d, J=7.6Hz), 7.66(1H, d, J=8.6Hz)

Table 67

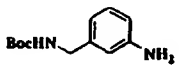
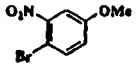
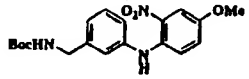
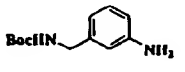
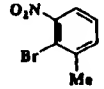
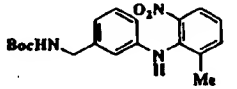
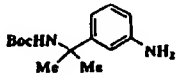
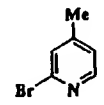
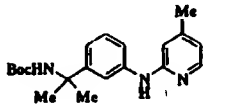
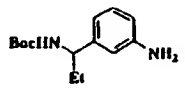
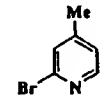
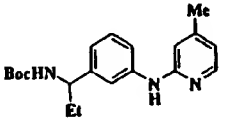
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
427				Pd : (1) base: (1)	^{1}H-NMR($CDCl_3$) δ 1.46(9H, s), 3.83(3H, s), 4.32(2H, d, J=5.9 Hz), 4.88(1H, brt), 7.03-7.12(3H, m), 7.15(1H, s), 7.23 (1H, s), 7.34(1H, dd, J=7.6, 7.6Hz), 7.63(1H, d, J=3.0Hz), 9.30(1H, brs)
428				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.44(9H, s), 2.09(3H, s), 4.24(2H, d, J=5.9 Hz), 4.80(1H, brt), 6.64(1H, d, J=7.9Hz), 6.66(1H, s), 6.87 (1H, d, J=7.6), 7.08(1H, dd, J=7.9, 7.9Hz), 7.19(1H, dd, J=7.6, 7.6Hz), 7.43(1H, d, J=7.6Hz), 7.97(1H, d, J=7.9Hz), 8.24(1H, brs)
429				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.37(9H, s), 1.63(6H, s), 2.24(3H, s), 4.99 (1H, brs), 6.56(1H, d, J=5.0Hz), 6.70(1H, s), 6.74(1H, brs), 7.09(1H, d, J=7.3Hz), 7.20-7.31(3H, m), 8.05(1H, d, J=5.0Hz)
430				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 0.92(3H, t, J=7.3Hz), 1.42(9H, s), 1.66-1.82(2H, m), 2.26(3H, s), 4.43-4.60(1H, m), 4.77-4.87(1H, m), 6.52(1H, brs), 6.58(1H, d, J=5.0Hz), 6.68(1H, s), 6.94 (1H, d, J=6.6Hz), 7.17(1H, s), 7.23-7.32(2H, m), 8.06(1H, d, J=5.0Hz)

Table 68

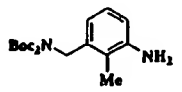
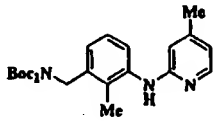
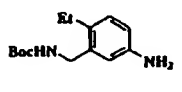
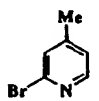
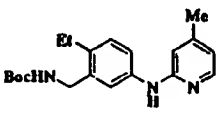
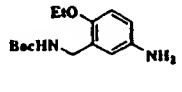
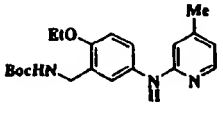
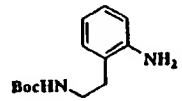
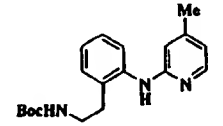
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
431				Pd : (2) base: (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(18H, s), 2.19(3H, s), 2.20(3H, s), 4.83(2H, s), 6.21(1H, brs), 6.27(1H, s), 6.52(1H, d, J=5.0 Hz), 6.60(1H, d, J=7.6Hz), 6.99(1H, d, J=7.6Hz), 7.18(1H, dd, J=7.6, 7.6Hz), 7.24(1H, s), 8.02(1H, d, J=5.0Hz)
432				Pd : (2) base: (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.23(3H, t, J=7.3Hz), 1.46(9H, s), 2.25(3H, s), 2.64(2H, q, J=7.3Hz), 4.33(2H, q, J=5.3Hz), 4.71(1H, brt), 6.44(1H, brs), 6.56(1H, d, J=5.3Hz), 6.64(1H, s), 7.14-7.26(3H, m), 8.04(1H, d, J=5.3Hz)
433				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.44(3H, t, J=6.9Hz), 1.44(9H, s), 2.22(3H, s), 4.06(2H, q, J=6.9Hz), 4.31(2H, d, J=5.6Hz), 5.02(1H, brt), 6.31(1H, brs), 6.50(1H, s), 6.51(1H, d, J=5.3Hz), 6.83(1H, d, J=8.6Hz), 7.16-7.23(2H, m), 8.01(1H, d, J=5.3 Hz)
434				Pd : (2) base: (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.44(9H, s), 2.22(3H, s), 2.78-2.86(2H, m), 3.25-3.34(2H, m), 4.78(1H, brt), 6.54(1H, d, J=5.3Hz), 6.58(1H, s), 6.86(1H, brs), 7.01-7.13(1H, m), 7.17-7.28(2H, m), 7.66-7.75(1H, m), 8.03(1H, d, J=5.3Hz)

Table 69

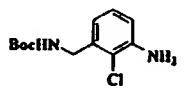
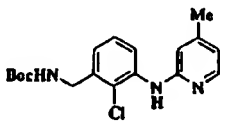
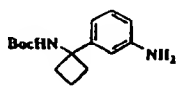
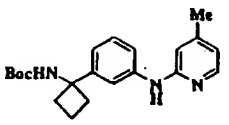
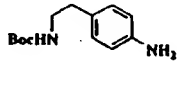
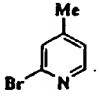
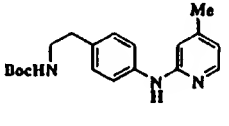
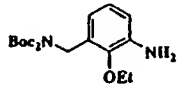
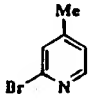
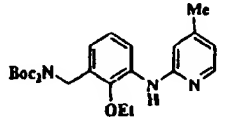
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
435				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(9H, s), 2.29(3H, s), 4.42(2H, d, J=5.6 Hz), 4.96(1H, brt), 6.66(1H, d, J=5.0Hz), 6.69(1H, s), 6.81 (1H, brs), 7.02(1H, d, J=7.3Hz), 7.23(1H, dd, J=7.3, 7.3Hz), 7.96(1H, d, J=7.3Hz), 8.12(1H, d, J=5.0Hz)
436				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.36(9H, brs), 1.80-1.95(1H, m), 2.01-2.17(1H, m), 2.45-2.60(4H, m), 5.09(1H, brs), 6.56(1H, brs), 6.57(1H, d, J=5.3Hz), 6.70(1H, s), 7.11(1H, d, J=7.3 Hz), 7.22-7.31(3H, m), 8.05(1H, d, J=5.3Hz)
437				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.44(9H, s), 2.25(3H, s), 2.72-2.79(2H, m), 3.32-3.42(2H, m), 4.56(1H, brt), 6.47(1H, brs), 6.56(1H, d, J=4.9Hz), 6.65(1H, s), 7.10-7.19(2H, m), 7.22-7.30(2H, m), 8.05(1H, d, J=4.9Hz)
438				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.40(3H, t, J=6.9Hz), 1.44(18H, s), 2.28(3H, s), 3.91(2H, q, J=6.9Hz), 4.89(2H, s), 6.60(1H, d, J=5.0 Hz), 6.68(1H, s), 6.77(1H, s), 6.79(1H, d, J=7.9Hz), 7.05(1H, dd, J=7.9, 7.9Hz), 7.77(1H, d, J=7.9Hz), 8.09(1H, d, J= 5.0Hz)

Table 70

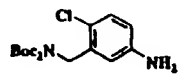
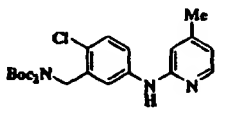
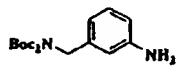
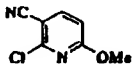
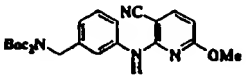
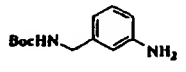
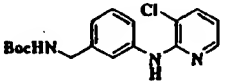
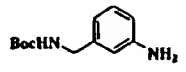
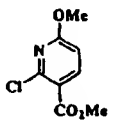
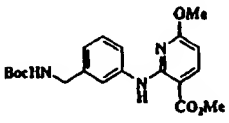
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
439				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR(CDCl$_3$) δ 1.44(18H, s), 2.26(3H, s), 4.88(2H, s), 6.45(1H, brs), 6.59(1H, d, J=5.3Hz), 6.62(1H, s), 7.08(1H, s), 7.25-7.29(2H, m), 8.05(1H, d, J=5.3Hz)
440				Pd : (1) base : (3)	^{1}H-NMR(CDCl$_3$) δ 1.45(18H, s), 3.93(3H, s), 4.78(2H, s), 6.22(1H, d, J=8.6Hz), 7.00(1H, s), 7.03(1H, d, J=7.6Hz), 7.29(1H, dd, J=7.6, 7.6Hz), 7.46(1H, d, J=7.6Hz), 7.54(1H, s), 7.62(1H, d, J=8.6Hz)
441				Pd : (2) base : (2) ligand : (1)	^{1}H-NMR(CDCl$_3$) δ 1.47(9H, s), 4.32(2H, d, J=5.6Hz), 4.86(1H, brs), 6.71(1H, dd, J=7.6, 5.0Hz), 6.97(1H, d, J=7.6Hz), 6.98(1H, s), 7.30(1H, dd, J=7.6, 7.6Hz), 7.52-7.60(3H, m), 8.12(1H, dd, J=5.0, 1.7Hz)
442				Pd : (1) base : (3)	^{1}H-NMR(CDCl$_3$) δ 1.47(9H, s), 3.89(3H, s), 3.98(3H, s), 4.32(2H, d, J=5.4Hz), 4.81(1H, brt), 6.15(1H, d, J=8.5Hz), 6.96(1H, d, J=8.3Hz), 7.28(1H, dd, J=8.3, 8.3Hz), 7.57(1H, d, J=8.3Hz), 7.77(1H, s), 8.11(1H, d, J=8.5Hz), 10.47(1H, s)

Table 71

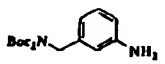
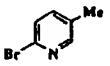
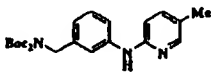
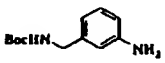
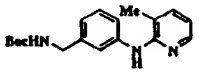
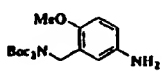
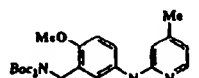
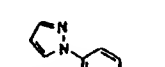
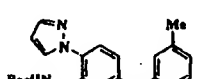
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
497				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(18H, s), 2.23(3H, s), 4.76(2H, s), 6.50(1H, brs), 6.83(1H, d, J=6.9Hz), 6.93(1H, d, J=6.9Hz), 7.15-7.36(4H, m), 8.02(1H, s)
498				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.46(9H, s), 2.24(3H, s), 4.30(2H, d, J=5.6Hz), 4.83(1H, br1), 6.13(1H, brs), 6.72(1H, dd, J=7.3, 5.0Hz), 6.91(1H, d, J=7.3Hz), 7.27(1H, dd, J=7.6, 7.6Hz), 7.36(1H, d, J=7.6Hz), 7.46(1H, s), 7.48(1H, d, J=7.6Hz), 8.11(1H, d, J=5.0Hz)
499				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.43(18H, s), 2.20(3H, s), 3.82(3H, s), 4.81(2H, s), 6.27(1H, brs), 6.46(1H, s), 6.50(1H, d, J=5.3Hz), 6.83(1H, d, J=8.9Hz), 7.00(1H, d, J=2.3Hz), 7.18(1H, dd, J=8.9, 2.3Hz), 8.00(1H, d, J=5.3Hz)
500				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 1.44(9H, s), 2.29(3H, s), 4.11(2H, d, J=6.6Hz), 5.72(1H, br1), 6.42-6.46(1H, m), 6.60-6.73(3H, m), 7.24(1H, d, J=8.6Hz), 7.39-7.45(1H, m), 7.41(1H, s), 7.50-7.58(1H, m), 7.64(1H, d, J=2.0Hz), 7.72(1H, d, J=1.3Hz), 8.09(1H, d, J=5.3Hz)

Table 72

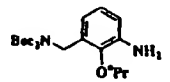
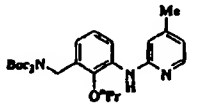
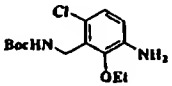
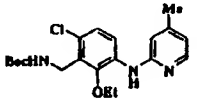
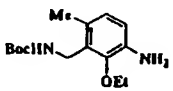
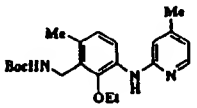
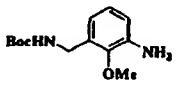
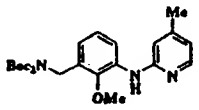
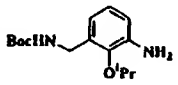
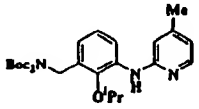
Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
505				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR(CDCl$_3$) δ 8.09(1H, d, J=5.3Hz), 7.80(1H, d, J=7.9Hz), 7.05(1H, dd, J=7.9, 7.9Hz), 6.83-6.72(2H, m), 6.66(1H, s), 6.59(1H, d, J=5.3Hz), 4.90(2H, s), 3.78(2H, t, J=6.6Hz), 2.28(3H, s), 1.90-1.75(2H, m), 1.44(18H, s), 1.06(3H, t, J=7.3Hz)
519				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR(CDCl$_3$) δ 1.45(3H, t, J=6.9Hz), 1.45(9H, s), 2.29(3H, s), 3.94(2H, q, J=6.9Hz), 4.52(1H, d, J=5.6Hz), 4.94(1H, brt), 6.58(1H, s), 6.62(1H, d, J=5.0Hz), 6.74(1H, brs), 7.12(1H, d, J=8.9Hz), 8.00(1H, d, J=8.9Hz), 8.10(1H, d, J=5.0Hz)
520				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR(CDCl$_3$) δ 1.40(3H, t, J=6.9Hz), 1.45(9H, s), 2.26(3H, s), 2.35(3H, s), 3.88(2H, q, J=6.9Hz), 4.39(2H, d, J=5.0Hz), 4.76(1H, brs), 6.58(1H, d, J=5.3Hz), 6.61(1H, s), 6.93(1H, d, J=8.2Hz), 7.65(1H, d, J=8.2Hz), 8.07(1H, d, J=5.3Hz)

Table 73

Example	Aniline derivative	Halogenated derivative	Product	Reaction conditions	Spectral data
540				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 8.10(1H, d, J=5.3Hz), 7.80(1H, d, J=7.3Hz), 7.06(1H, dd, J=8.6, 7.3Hz), 6.81(1H, s), 6.77(1H, d, J=8.6Hz), 6.69(1H, s), 6.60(1H, d, J=5.3Hz), 4.89(2H, s), 3.75(3H, s), 2.28(3H, s), 1.45(18H, s)
542				Pd : (2) base : (1) ligand : (1)	^{1}H-NMR($CDCl_3$) δ 8.09(1H, d, J=5.3Hz), 7.74(1H, d, J=7.6Hz), 7.04(1H, dd, J=8.6, 7.6Hz), 6.80(1H, d, J=8.6Hz), 6.74(1H, s), 6.67(1H, s), 6.58(1H, d, J=5.3Hz), 4.88(2H, s), 4.19-4.07(1H, m), 2.27(3H, s), 1.43(18H, s), 1.29(6H, d, J=6.3Hz)

Example 45

Synthesis of 2-(3-aminomethylphenylamino)-6-methoxynicotinic acid hydrochloride

[0069] A mixture of the compound (37 mg) obtained in Example 43, potassium hydroxide (96 mg), water (2 ml) and 1,4-dioxane (2 ml) was heated at 60°C for 2 h. The reaction mixture was cooled, then rendered acidic with 2 N HCl and subjected to extraction with methylene chloride. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was worked up as in Example 2 to give the titled compound quantitatively.

^{1}H-NMR (DMSO-d_6)
δ:3.95(3H, s), 4.01(2H, brs), 6.27(1H, d, J=8.6Hz), 7.14(1H, d, J=7.6Hz), 7.39(1H, dd, J=8.3, 7.6Hz), 7.71(1H, s), 7.90(1H, d, J=8.3Hz), 8.14(1H, d, J=8.6Hz), 8.30(3H, brs), 10.75 (1H, s), 13.06(1H, brs)

Example 52

Synthesis of 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine hydrochloride

[0070] A mixture of the compound (118 mg) obtained in Example 446, concentrated sulfuric acid (1 ml) and water (2 ml) was heated at 120°C for 4 h. The reaction mixture was put into ice water, adjusted to pH 8 with saturated sodium hydrogencarbonate and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and dried under reduced pressure. The resulting residue was dissolved in methanol (2 ml) and, after addition of a 1,4-dioxane solution (4 N, 0.5 ml) of hydrogen chloride at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was recrystallized from methanol-ethyl acetate to give 37.1 mg of the titled compound (61%).

^{1}H-NMR (DMSO-d_6)
δ:2.49(3H, s), 4.03(2H, q, J=5.6Hz), 6.90(1H, d, J=8.6Hz), 7.27(1H, d, J=7.9Hz), 7.42(1H, dd, J=7.9, 7.9Hz), 7.77 (1H, s), 7.86(1H, d, J=7.9Hz), 8.31(3H, brs), 8.45 (1H, d, J=8.6Hz), 10.09(1H, s)

Example 53

Synthesis of 2-(3-aminomethylphenylamino)-6-ethyl-3-nitropyridine hydrochloride

[0071] Using the compound obtained in Example 447 as a starting material, the procedure of Example 52 was repeated to give the titled compound (yield, 85%).

^{1}H-NMR (DMSO-d_6)
δ:1.24(3H, t, J=7.3Hz), 2.79(2H, q, J=7.3Hz), 4.02(2H, q, J=5.0Hz), 6.92(1H, d, J=8.6Hz), 7.26(1H, d, J=7.6Hz), 7.43 (1H, dd, J=7.6, 7.6Hz), 7.75(1H, s), 7.90(1H, d, J=7.6Hz), 8.41(3H, brs), 8.48(1H, d, J=8.6Hz), 10.10(1H, s)

Example 443

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxy-isonicotinic acid

[0072] To a mixture of the compound (53.8 mg) obtained in Example 423 and methanol (3 ml), a 2N aqueous sodium hydroxide solution (1 ml) was added. The reaction mixture was stirred at room temperature for 4 h and concentrated under reduced pressure. To the resulting residue, ethyl acetate was added and mixture was subjected to extraction with water. The aqueous layer was adjusted to pH 1 with 2N HCl and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 47.3 mg of the titled compound (yield, 90%).

^{1}H-NMR($CDCl_3$)
δ:7.49(1H, d, J=7.9Hz), 7.45(1H, s), 7.28(1H, dd, J=7.9, 7.3Hz), 6.98(1H, s), 6.93(1H, d, J=7.3Hz), 6.76(1H, s), 4.92(1H, brs), 4.31(2H, d, J=5.6Hz), 3.95(3H, s), 1.46(9H, s)

Example 444

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-hydroxymethyl-6-methoxypyridine

[0073] To a mixture of the compound (155.3 mg) obtained in Example 423, tetrahydrofuran (4 ml) and methanol (2 ml), lithium borohydride (13 mg) was added. The reaction mixture was stirred at room temperature for one week and, after addition of water, the mixture was concentrated under reduced pressure. Water was added to the resulting residue and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 1) to give 86.1 mg of the titled compound (yield, 60%).

^{1}H-NMR($CDCl_3$)
δ: 7.37(1H, s), 7.18-7.12(2H, m), 6.93-6.88(1H, m), 6.42(1H, s), 6.42(1H, s), 6.18(1H, s), 4.88(1H, brs), 4.59(2H, s), 4.29(2H, d, J=5.6Hz), 3.90(3H, s), 1.45(9H, s)

Example 446

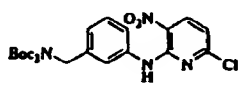
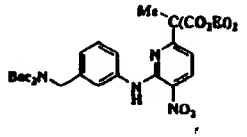
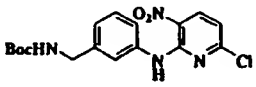
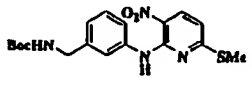
Synthesis of 2-(2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-3-nitropyridine-6-yl)malonic acid dimethyl ester

[0074] To a mixture of the compound (150 mg) obtained in Example 27, dimethyl malonate (50 mg) and dimethyl-formamide (3 ml), sodium hydride (content, 60%; 15 mg) was added. The reaction mixture was stirred at room temperature for 3 h and then ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, n-hexane:ethyl acetate = 2 : 1) to give 123 mg of the titled compound (yield, 68%).

^{1}H-NMR($CDCl_3$)
δ:1.47(18H, s), 3.76(6H, s), 4.81(2H, s), 4.91(1H, s), 6.95(1H, d, J=8.6Hz), 7.08(1H, d, J=7.9Hz), 7.32(1H, dd, J=7.9, 7.9Hz), 7.44(1H, s), 7.68(1H, d, J=7.9Hz), 8.54(1H, d, J=8.6Hz), 10.18(1H, brs)

[0075] The procedure of Example 446 was repeated using corresponding chlorinated derivatives forms and corresponding reagents to give the compounds listed in Table 74.

Table 74

Example	Chlorinated derivative	Reagent	Product	Spectral data
447		$CH_3CH(CO_2Et)_2$		^{1}H-NMR($CDCl_3$) δ 1.15-1.23(6H, m), 1.47(18H, s), 1.85(3H, s), 4.10-4.40(4H, m), 4.81(2H, s), 6.97(1H, d, J=8.9Hz), 7.07(1H, d, J=7.6Hz), 7.31(1H, dd, J=7.6, 7.6Hz), 7.34(1H, d, J=2.0Hz), 7.62-7.69(1H, m), 8.51(1H, d, J=8.9Hz), 10.17(1H, brs)
448		MeSH		^{1}H-NMR($CDCl_3$) δ 1.47(9H, s), 2.53(3H, s), 4.35(2H, d, J=5.6Hz), 4.85(1H, brt), 6.68(1H, d, J=8.9Hz), 7.10(2H, d, J=7.6Hz), 7.34(1H, dd, J=7.6, 7.6Hz), 7.52(1H, d, J=7.6Hz), 7.60(1H, s), 8.27(1H, d, J=8.9Hz), 10.45(1H, brs)

Example 449

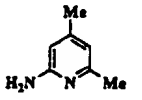
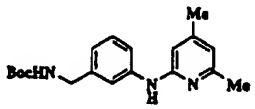
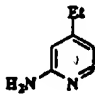
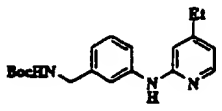
Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-methylpyridine

[0076] A mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)bromobenzene (260 mg), tris(dibenzylideneacetone)dipalladium (42 mg), diphenylphosphinoferrocene (50 mg), potassium t-butoxide (102 mg), 2-amino-4-methylpyridine (108 mg) and toluene (10 ml) was heated under a nitrogen atmosphere at 80°C for 22 h. Ethyl acetate and water were added to the reaction mixture. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 1) to give 29.2 mg of the titled compound (yield, 10%).

^{1}H-NMR($CDCl_3$)
δ:1.46(9H, s), 2.26(3H, s), 4.30(2H, d, J=5.9Hz), 4.90(1H, brt), 6.59(1H, d, J=5.0Hz), 6.60(1H, s), 6.68(1H, s), 6.94(1H, d, J=6.3Hz), 7.21-7.31(3H, m), 8.06(1H, d, J=5.0Hz)

[0077] The procedure of Example 449 was repeated using corresponding amine derivatives to give the compounds listed in Table 75.

Table 75

Example	Amine derivative	Product	Spectral data
450			^{1}H-NMR($CDCl_3$) δ 1.46(9H, s), 2.22(3H, s), 2.40(3H, s), 4.30(2H, d, J=5.6Hz), 4.83(1H, brt), 6.43(1H, brs), 6.47(1H, s), 6.53(1H, s), 6.93(1H, d, J=7.3Hz), 7.19-7.29(3H, m)
451			^{1}H-NMR($CDCl_3$) δ 1.21(3H, t, J=7.6Hz), 1.46(9H, s), 2.56(2H, q, J=7.6Hz), 4.30(2H, d, J=5.6Hz), 4.83(1H, brt), 6.54(1H, brs), 6.61(1H, d, J=5.0Hz), 6.69(1H, s), 6.91-6.95(1H, m), 7.18-7.31(3H, m), 8.09(1H, d, J=5.0Hz)

Example 452

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxynicotinic acid

[0078] Using the compound obtained in Example 442 as a starting material, the procedure of Example 45 was repeated to give the titled compound (yield, 92%).

^{1}H-NMR($CDCl_3$-CD_3OD)
δ:1.46(9H, s), 3.99(3H, s), 4.30(2H, s), 6.16(1H, d, J=8.6Hz), 6.94(1H, d, J=7.8Hz), 7.28(1H, dd, J=7.8, 7,8Hz), 7.58(1H, d, J=7,8Hz), 7.73(1H, s), 8.16(1H, d, J=8.6Hz)

Example 453

Synthesis of 2-(3-t-butoxycarbonylaminomethyl)phenylamino)-6-methoxynicotinamide

[0079] To a mixture of the compound (44 mg) obtained in Example 452, triethylamine (18 mg) and tetrahydrofuran (2 ml), ethyl chlorocarbonate (14.3 mg) was added and the resulting mixture was stirred at room temperature for 15 min. Ammonia gas was blown through the reaction mixture at room temperature and after stirring at room temperature for 5 min, the mixture was concentrated under reduced pressure. To the resulting residue, a saturated aqueous sodium hydrogen-carbonate solution was added and the mixture was subjected to extraction with methylene chloride. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by preparative thin-layer chromatography (eluent, methanol:methylene chloride = 1 : 20) to give 10 mg of the titled compound (yield, 11%).

^{1}H-NMR(DMSO-d_6)
δ: 1.39 (9H, s), 3.92(3H, s), 4.12(2H, d, J=5.9Hz), 6.20(1H, d, J=8.6Hz), 6.85(1H, d, J=7.6Hz), 7.24(1H, dd, J=7.6, 7.6Hz), 7.32-7.40(2H, m), 7.51(1H, d, J=7.6Hz), 7.61(1H, s), 8.01(1H, brs), 8.10(1H, d, J=8.6Hz)

Example 454

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-3-hydroxymethyl-6-methoxypyridine

[0080] To a mixture of the compound (300 mg) obtained in Example 452, triethylamine (101 mg) and tetrahydrofuran (8 ml), a tetrahydrofuran solution (1 ml) of ethyl chlorocarbonate (109 mg) was added under ice cooling and the resulting mixture was stirred at 0°C for 15 min. The reaction mixture was filtered and a tetrahydrofuran solution (2 M, 0.8 ml) of lithium borohydride was added to the filtrate under ice cooling. The reaction mixture was stirred at 0°C for 30 min and thereafter a 1 N aqueous sodium hydroxide solution was added under ice cooling. Further, the reaction mixture was stirred at 0°C for 5 min and then ether and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:methylene chloride = 1 : 10) to give 199 mg of the titled compound (yield, 69%).

^{1}H-NMR($CDCl_3$)
δ: 1.46(9H, s), 3.93(3H, s), 4.31(2H, d, J=5.6Hz), 4.67(2H, d, J=5.6Hz), 4.79(1H, brt), 6.15(1H, d, J=7.9Hz), 6.89(1H, d, J=7.6Hz), 7.21-7.31(3H, m), 7.48(1H, d, J=7.6Hz), 7.64(1H, brs), 7.70(1H, brs)

Example 456

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-6-methoxypyridine-3-carboaldehyde

[0081] A mixture of the compound (24 mg) obtained in Example 454, manganese tetraoxide (40 mg) and benzene (8 ml) was stirred at room temperature for 2 days.

[0082] The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:methylene chloride = 1 : 20) to give 14 mg of the titled compound (yield, 59%).

^{1}H-NMR($CDCl_3$)
δ:1.47(9H, s), 4.01(3H, s), 4.33(2H, d, J=5.6Hz), 4.82(1H, brt), 6.24(1H, d, J=8.3Hz), 7.00(1H, d, J=7.6Hz), 7.30(1H, dd, J=7.6, 7.6Hz), 7.61(1H, d, J=7.6Hz), 7.71(1H, d, J=8.3Hz), 7.72(1H, s), 9.67(1H, s), 10.95(1H, s)

Example 472

Synthesis of 2-(3-aminomethylphenylamino)-4-hydroxymethyl-6-methoxypyridine dihydrochloride

[0083] To a mixture of the compound (109.5 mg) obtained in Example 423, tetrahydrofuran (4 ml) and methanol (1

ml), lithium borohydride (19 mg) was added. The reaction mixture was stirred at room temperature for 44 h and after addition of 2 N HCl, the resulting mixture was concentrated under reduced pressure. The resulting residue was subjected to basic silica gel column chromatography (eluent, methanol:methylene chloride = 1 : 19). To a mixture of the purified product and methanol (3 ml), a 1,4-dioxane solution (4 N, 0.3 ml) of hydrogen chloride was added and the resulting mixture was concentrated under reduced pressure. The resulting residue was recrystallised from methanol-ethyl acetate to give 48 mg of the titled compound (yield, 58%).

^{1}H-NMR(DMSO-d_6)
δ:9.18(1H, brs), 8.39(3H, brs), 7.78(1H, s), 7.61(1H, d, J=7.9Hz), 7.29(1H, dd, J=7.9, 7.3Hz), 7.08(1H, brs), 7.02(1H, d, J=7.3Hz), 6.47(1H, s), 6.11(1H, s), 4.42(2H, s), 3.94(2H, q, J=5.6Hz), 3.87(3H, s)

Example 507

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-5-methylthiazole

[0084] To a mixture of propionaldehyde (72 µl), chloroform (1 ml) and 1,4-dioxane (1 ml), bromine (52 µl) was added. The reaction mixture was stirred at room temperature for 30 min and then N-(3-(t-butoxycarbonylaminomethyl)phenyl)thiourea (262 mg), acetone (2 ml) and triethylamine (0.14 ml) were added. The reaction mixture was heated under reflux for 3.5 h and concentrated under reduced pressure. To the resulting residue, water was added and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, methylene chloride:methanol = 99 : 1) to give 79.2 mg of the titled compound (yield, 27%).

^{1}H-NMR($CDCl_3$)
δ:7.30-7.22(4H, m), 7.17(1H, d, J=7.6Hz), 6.91(1H, d, J=1.0Hz), 4.94(1H, brs), 4.30(2H, d, J=5.6Hz), 2.34(3H, d, J=1.0Hz), 1.47(9H, s)

Example 508

Synthesis of 2-(3-aminomethylphenylamino)-5-methylthiazole

[0085] A mixture of the compound (73 mg) obtained in Example 507 and trifluoroacetic acid (5 ml) was stirred at room temperature for 1 h and concentrated under reduced pressure. The resulting residue was purified by basic silica gel column chromatography (eluent, methylene chloride methanol = 95 : 5) to give 34.5 mg of the titled compound (yield, 67%).

^{1}H-NMR($CDCl_3$)
δ:7.32-7.28(3H, m), 7.19(1H, d, J=7.3Hz), 6.97(1H, d, J=7.3Hz), 6.92(1H, d, J=1.0Hz), 3.87(2H, s), 2.35(3H, d, J=1.0Hz), 1.76(2H, brs)

Example 509

Synthesis of 2-(3-(t-butoxycarbonylaminomethyl)phenylamino)-4-methylthiazole

Example 511

Synthesis of 2-(3-(di-(t-butoxycarbonyl)aminomethyl)phenylamino)-5-methyloxazole

[0086] To a mixture of 3-(di-(t-butoxycarbonyl)aminomethyl)aniline (200 mg), dimethylaminopyridine (166 mg) and methylene chloride (10 ml), thiophosgene (45 µl) was added under ice cooling and the resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 3) to give N-(3-(di-(t-butoxycarbonyl)aminomethyl)phenyl)isothiocyanate.

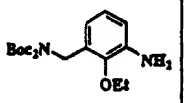
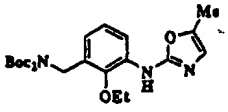
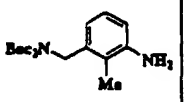
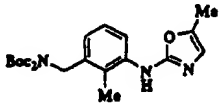
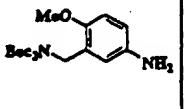
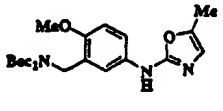
[0087] A mixture of the thus obtained compound (193 mg), 1-azido-propane-2-one (81 mg), triphenylphosphine (217 mg) and methylene chloride (5 ml) was stirred at room temperature for 15 h and then oxalic acid (115 mg) was added at room temperature. The reaction mixture was heated under stirring at 60°C for 30 min and concentrated under reduced pressure. To the resulting residue, ethyl acetate and a 2 N aqueous sodium hydroxide solution were added.

The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 10) to give 78 mg of the titled compound (yield, 33%).

^{1}H-NMR($CDCl_3$)
δ:1.45(18H, s), 2.25(3H, d, J=1.0Hz), 4.77(2H, s), 6.51(1H, d, J=1.0Hz), 6.91(1H, d, J=7.6Hz), 7.15(1H, brs), 7.22-7.26(1H, m), 7.25(1H, dd, J=7.6, 7.6Hz), 7.40(1H, d, J=7.6Hz)

[0088] The procedure of Example 511 was repeated using corresponding reagents to give the compounds shown in Table 76.

Table 76

Example	Aniline derivative	Product	Spectral data
512			^{1}H-NMR($CDCl_3$) δ 1.43(18H, s), 1.46(3H, t, J=6.9Hz), 2.27(3H, d, J=1.0Hz), 3.93(2H, q, J=6.9Hz), 4.88(2H, s), 6.52(1H, d, J=1.0Hz), 6.77(1H, d, J=7.6Hz), 7.08(1H, dd, J=7.6, 7.6Hz), 7.19(1H, s), 8.02(1H, d, J=7.6Hz)
513			^{1}H-NMR($CDCl_3$) δ 1.44(18H, s), 2.21(3H, s), 2.24(3H, s), 4.82(2H, s), 6.48(1H, s), 6.88(1H, d, J=7.9Hz), 7.19(1H, dd, J=7.9, 7.9Hz), 7.77(1H, d, J=7.9Hz)
514			^{1}H-NMR($CDCl_3$) δ 1.44(18H, s), 2.23(3H, s), 3.79(3H, s), 4.80(2H, s), 6.46(1H, s), 6.81(1H, d, J=8.9Hz), 6.97(1H, d, J=2.3Hz), 7.45(1H, dd, J=8.9, 2.3Hz)

Example 515

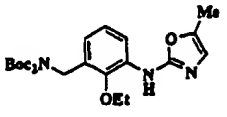
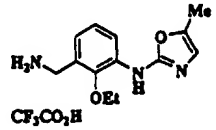
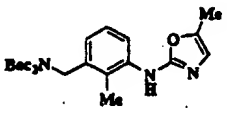
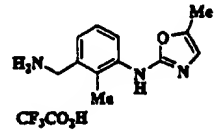
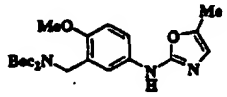
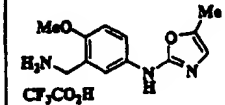
Synthesis of 2-(3-aminomethyl)phenylamino)-5-methyloxazole trifluoroacetic acid salt

[0089] A mixture of the compound (292 mg) obtained in Example 511 and trifluoroacetic acid (2 ml) was stirred at room temperature for 2 h and concentrated under reduced pressure. The resulting residue was recrystallised from ethanol/ethyl acetate/n-hexane to give 119 mg of the titled compound (38%).

^{1}H-NMR(DMSO-d_6)
δ:2.24(3H, s), 3.98(2H, q, J=5.6Hz), 6.59(1H, s), 7.00(1H, d, J=7.3Hz), 7.32(1H, dd, J=7.3, 7.3Hz), 7.53(1H, d, J=7.3Hz), 7.67(1H, s), 8.16(3H, brs), 10.08(1H, s)

[0090] The procedure of Example 515 was repeated using corresponding reagents to give the compounds listed in Table 77.

Table 77

Example	Reagent	Product	Spectral data
516			^{1}H-NMR(DMSO-d_6) δ 1.37(3H, t, J=6.9Hz), 2.24(3H, s), 3.89(2H, q, J=6.9Hz), 4.05(2H, q, J=5.6Hz), 6.63(1H, s), 7.08(1H, d, J=7.9Hz), 7.15(1H, dd, J=7.9, 7.9Hz), 8.13(1H, d, J=7.9Hz), 8.18(3H, brs), 9.33(1H, brs)
517			^{1}H-NMR(DMSO-d_6) δ 2.22(3H, s), 2.23(3H, s), 4.05(2H, q, J=5.6Hz), 6.60(1H, s), 7.12(1H, d, J=7.9Hz), 7.24(1H, dd, J=7.9, 7.9Hz), 7.75(1H, d, J=7.9Hz), 8.18(3H, brs), 9.40(1H, brs)
518			^{1}H-NMR(DMSO-d_6) δ 2.22(3H, s), 3.80(3H, s), 3.94(2H, q, J=5.6Hz), 6.55(1H, s), 7.02(1H, d, J=8.9Hz), 7.54(1H, dd, J=8.9, 2.3Hz), 7.59(1H, d, J=2.3Hz), 8.00(3H, brs), 9.87(1H, s)

Example 523

Synthesis of 2-(3-aminomethylphenylamino)-3,5-dinitropyridine

[0091] A mixture of 3-aminobenzylamine (696 mg), dimethylaminopyridine (674 mg), 3-nitrophenyloxycarbonyl-Wang resin (2.85 g; Tetrahedron Lett., Vol, 37, 937 (1996)) and tetrahydrofuran (60 ml) was stirred at room temperature for 24 h and then filtered. The resulting resin was washed sequentially with dimethylformamide, water, methanol and methylene chloride and then dried under reduced pressure to give 3-aminobenzylaminocarbonyl-Wang resin.

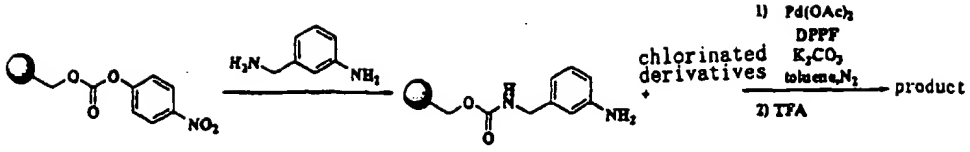
[0092] A mixture of the thus obtained resin (100 mg, 0.071 mol), potassium carbonate (100 mg), 2-chloro-3,5-dinitropyridine (72 mg), palladium (II) acetate (16 mg), diphenylphosphinoferrocene (79 mg) and acetonitrile (9 ml) was stirred under a nitrogen atmosphere at 80°C and then filtered. The resulting resin was washed sequentially with dimethylfor-

mamide, water, methanol and methylene chloride, dried under reduced pressure and, after adding trifluoroacetic acid, the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. To the resulting residue, water and ethyl acetate were added. The aqueous layer was washed with ethyl acetate and concentrated under reduced pressure. The resulting residue was purified with Sep-PaK^{R} Plus C18 Cartridges (Waters) to give 1.7 mg of the titled compound (8%).

^{1}H-NMR(CD_3OD)
δ:4.16(2H, s), 7.35(1H, d, J=7.9Hz), 7.53(1H, dd, J=7.9, 7.9Hz), 7.75(1H, d, J=7.9Hz), 7.80(1H, s), 9.25(1H, d, J=2.4Hz), 9.30(1H, d, J=2.4Hz)

[0093] The procedure of Example 523 was repeated using corresponding chlorinated derivatives to give the compounds listed in Tables 78 - 80.

Table 78



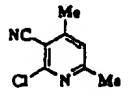
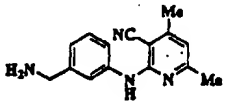
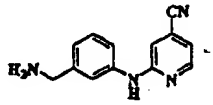
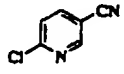
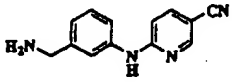
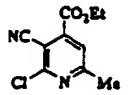
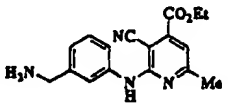
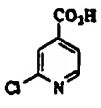
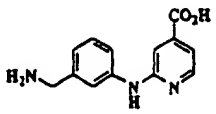
Example	Chlorinated derivative	Product	Spectral data
524			^{1}H-NMR(CD_3OD) 2.35(3H, s), 2.44(3H, s), 4.13(2H, s), 6.78(1H, s), 7.19-7.50(3H, m), 7.72(1H, d, J=2.0Hz)
525			^{1}H-NMR(CD_3OD) 4.18(2H, s), 7.33-7.46(4H, m), 7.51(1H, d, J=7.6Hz), 7.64(1H, dd, J=7.6, 7.6Hz), 8.45(1H, d, J=5.0Hz)
526			^{1}H-NMR(CD_3OD) 4.17(2H, s), 7.29(1H, d, J=8.7Hz), 7.34(1H, d, J=7.6Hz), 7.39(1H, s), 7.53(1H, d, J=7.6Hz), 7.64(1H, dd, J=7.6, 7.6Hz), 8.04(1H, dd, J=8.7, 2.0Hz), 8.61(1H, d, J=2.0Hz)
527			^{1}H-NMR(CD_3OD) 1.47(3H, t, J=7.3Hz), 2.56(3H, s), 4.14(2H, s), 4.48(2H, q, J=7.3Hz), 7.27(1H, d, J=7.9Hz), 7.30(1H, s), 7.46(1H, dd, J=7.9, 7.9Hz), 7.74(1H, s), 7.75(1H, d, J=7.9Hz)
528			^{1}H-NMR(CD_3OD) 4.12(2H, s), 7.02-7.12(2H, m), 7.26(1H, d, J=5.2Hz), 7.37-7.42(2H, m), 7.81(1H, s), 8.18(1H, d, J=5.2Hz)

Table 79

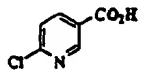
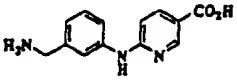
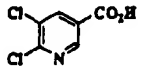
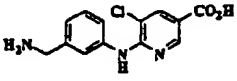
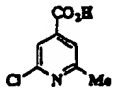
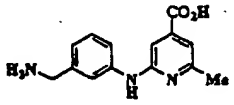
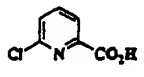
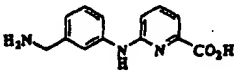
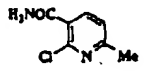
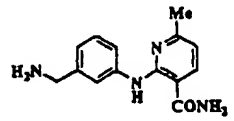
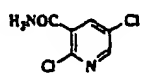
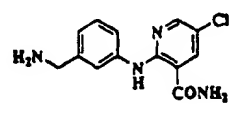
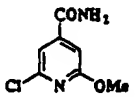
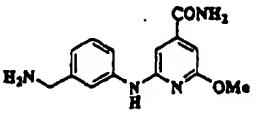
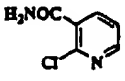
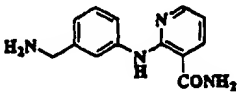
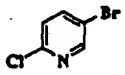
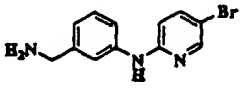
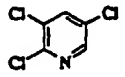
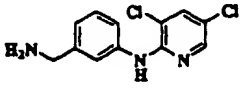
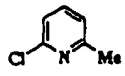
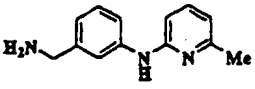
Example	Chlorinated derivative	Product	Spectral data
529			^{1}H-NMR (CD_3OD) 4.15 (2H, s), 6.87 (1H, d, J=8.7Hz), 7.14 (1H, d, J=7.4Hz), 7.43 (1H, dd, J=7.4, 6.9Hz), 7.53 (1H, d, J=6.9Hz), 7.98 (1H, s), 8.11 (1H, J=8.7, 2.1Hz), 8.81 (1H, d, J=2.1Hz)
530			^{1}H-NMR (CD_3OD) 4.16 (2H, s), 7.22 (1H, d, J=7.9Hz), 7.47 (1H, dd, J=7.9, 7.9Hz), 7.65 (1H, d, J=7.9Hz), 7.92 (1H, s), 8.22 (1H, d, J=2.0Hz), 8.69 (1H, d, J=2.0Hz)
531			^{1}H-NMR (CD_3OD) 2.49 (3H, s), 4.12 (2H, s), 7.05 (1H, d, J=6.2Hz), 7.15 (1H, s), 7.25 (1H, s), 7.38-7.42 (2H, m), 7.72 (1H, s)
532			^{1}H-NMR (CD_3OD) 4.14 (2H, s), 6.82 (1H, d, J=8.9Hz), 7.10 (1H, d, J=6.6Hz), 7.41-7.45 (2H, m), 8.02 (1H, s), 8.11 (1H, dd, J=8.9, 2.0Hz), 8.78 (1H, d, J=2.0Hz)
533			^{1}H-NMR (CD_3OD) 2.50 (3H, s), 4.12 (2H, s), 6.84 (1H, d, J=7.6Hz), 7.20 (1H, d, J=7.0Hz), 7.40 (1H, dd, J=7.0, 7.0Hz), 7.74-7.80 (2H, m), 7.87 (1H, d, J=7.6Hz)
534			^{1}H-NMR (CD_3OD) 4.15 (2H, s), 7.21 (1H, d, J=7.6Hz), 7.46 (1H, dd, J=7.6, 7.6Hz), 7.61 (1H, d, J=7.6Hz), 7.75 (1H, s), 8.11 (1H, d, J=2.6Hz), 8.35 (1H, d, J=2.6Hz)

Table 80

Example	Chlorinated derivative	Product	Spectral data
535			^{1}H-NMR (CD_3OD) 4.00 (3H, s), 4.12 (2H, s), 6.58 (1H, d, J=1.0Hz), 6.81 (1H, d, J=1.0 Hz), 7.09 (1H, d, J=6.9Hz), 7.37-7.43 (1H, m), 7.53 (1H, d, J=6.9Hz), 7.83 (1H, s)
536			^{1}H-NMR (CD_3OD) 4.15 (2H, s), 6.83-6.89 (1H, m), 6.96 (1H, dd, J=7.6, 3.9Hz), 7.21 (1H, d, J=7.6Hz), 7.46 (1H, dd, J=7.6, 7.6 Hz), 7.62 (1H, d, J=7.6Hz), 7.76 (1H, s), 8.02 (1H, dd, J=7.6, 1.6Hz), 8.37 (1H, dd, J=3.9, 1.6Hz)
537			^{1}H-NMR (CD_3OD) 4.12 (2H, s), 6.82 (1H, d, J=9.0Hz), 7.08 (1H, d, J=7.6Hz), 7.38 (1H, dd, J=7.6, 7.6Hz), 7.50 (1H, d, J=7.6Hz), 7.71 (1H, dd, J=9.0, 2.3Hz), 7.90 (1H, s), 8.22 (1H, d, J=2.3Hz)
538			^{1}H-NMR (CD_3OD) 4.13 (2H, s), 7.16 (1H, d, J=7.6Hz), 7.43 (1H, dd, J=7.6, 7.6Hz), 7.64 (1H, d, J=7.6Hz), 7.84 (1H, s), 7.87 (1H, d, J=2.3Hz), 8.10 (1H, d, J=2.3Hz)
539			^{1}H-NMR (CD_3OD) 2.48 (3H, s), 4.13 (2H, s), 6.72-6.80 (2H, m), 7.35-7.42 (1H, m), 7.44 (1H, s), 7.51-7.60 (1H, m), 7.68 (1H, dd, J=7.9, 7.9Hz), 7.74 (1H, s)

[0094] Several compounds used in the reactions described above are novel and the methods of synthesizing these compounds are described below as Examples 25e, 417e, 500b, 519e, 520d, 538e and 542a.

Example 25e

Synthesis of 2-(5-amino-2-ethylphenyl)-2-(t-butoxycarbonylamino)indane

[Example 25a]

Synthesis of 3-cyanomethyl-4-ethylnitrobenzene

[0095] To a mixture of 3-chloromethyl-4-ethylnitrobenzene (4.0 g) and dimethyl sulfoxide (50 ml), sodium cyanide (982 mg) was added. The reaction mixture was stirred at room temperature for 3 h and then ethyl acetate, n-hexane and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound quantitatively.

^{1}H-NMR($CDCl_3$)
δ:1.33(3H, t, J=7.6Hz), 2.78(2H, q, J=7.6Hz), 3.80(2H, s), 7.44(1H, d, J=8.6Hz), 8.18(1H, dd, J=8.6, 2.3Hz), 8.35(1H, d, J=2.3Hz)

[Example 25b]

Synthesis of 2-cyano-2-(2-ethyl-5-nitrophenyl)indane

[0096] To a mixture of the compound (3.0 g) obtained in Example 25a, α,α'-dichloro-o-xylene (4.15 g) and dimethyl sulfoxide (200 ml), potassium t-butoxide (3.55 g) was added and after stirring the resulting mixture at room temperature for 3h, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound (1.36 g) (yield, 29%).

^{1}H-NMR($CDCl_3$)
δ:1.45(3H, t, J=7.6Hz), 3.11(2H, q, J=7.6Hz), 3.61(2H, d, J=15.5Hz), 3.91(2H, d, J=15.5Hz), 7.25-7.33(4H, m), 7.53(1H, d, J=9.2Hz), 8.12-8.16(2H, m)

[Example 25c]

Synthesis of 2-(2-ethyl-5-nitrophenyl)-2-indaneamide

[0097] To a mixture of the compound (1.16 g) obtained in Example 25b and acetic acid (10 ml), water (2 ml) and concentrated sulfuric acid (20 ml) were added sequentially. The reaction mixture was heated under reflux for 13 h, cooled, put into ice water and subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give the titled compound (870 mg) (yield, 71%).

^{1}H-NMR($CDCl_3$)
δ:1.35(3H, t, J=7.6Hz), 2.82(2H, q, J=7.6Hz), 3.36(2H, d, J=15.9Hz), 3.95(2H, d, J=15.9Hz), 5.13(1H, brs), 5.43(1H, brs), 7.15-7.25(4H, m), 7.49(1H, d, J=8.3Hz), 8.08(1H, dd, J=8.3, 2.3Hz), 8.17(1H, d, J=2.3Hz)

[Example 25d]

Synthesis of 2-(t-butoxycarbonylamino)-2-(2-ethyl-5-nitrophenyl)indane

[0098] To a mixture of the compound (815 mg) obtained in Example 25c and t-butanol (12 ml), lead tetracetate (1.40 g) was added. The reaction mixture was heated under reflux for 3 h, cooled and, after adding water, subjected to extraction with ethyl acetate-ethylene glycol. The organic layer was washed with water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, chloroform) to give the titled compound (620 mg) (yield, 62%).

^{1}H-NMR($CDCl_3$)
δ:1.30(3H, t, J=7.6Hz), 1.31(9H, s), 2.93(2H, q, J=7.6Hz), 3.55(2H, d, J=15.9Hz), 3.63(2H, d, J=15.9Hz), 5.18(1H, s), 7.20-7.29(4H, m), 7.40(1H, d, J=8.6Hz), 8.05(1H, dd, J=8.6, 2.3Hz), 8.32(2H, d, J=2.3Hz)

[Example 25e]

Synthesis of 2-(5-amino-2-ethylphenyl)-2-(t-butoxycarbonylamino)indane

[0099] Using the compound obtained in Example 25d as a starting material, the procedure of Example 3 was repeated to give the titled compound (yield, 97%).

^{1}H-NMR($CDCl_3$)
δ:1.23(3H, t, J=7.6Hz), 1.30(9H, s), 2.74(2H, q, J=7.6Hz), 3.48-3.67(6H, m), 5.02(1H, s), 6.56(1H, dd, J=8.3, 2.3Hz), 6.74(1H, d, J=2.3Hz), 7.03(1H, d, J=8.3Hz), 7.15-7.24(4H, m)

Example 417e

Synthesis of N-(3-amino-2-ethoxyphenylmethyl)iminodicarboxylic acid di-t-butyl ester

[Example 417a]

Synthesis of 2-ethoxy-3-nitrobenzoic acid ethyl ester

[0100] To a mixture of 3-nitrosalicylic acid (5.0 g), ethyl iodide (11 ml) and dimethylformamide (200 ml), potassium carbonate (9.4 g) was added. The reaction mixture was stirred at 60°C for 4.5 h and, after adding water, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 1) to give 5.66 g of the titled compound (yield, 87%).

^{1}H-NMR($CDCl_3$)
δ:8.01(1H, dd, J=7.9, 1.7Hz), 7.89(1H, dd, J=7.9, 1.7Hz), 7.26(1H, dd, J=7.9, 7.9Hz), 4.42(2H, q, J=7.3Hz), 4.18(2H, q, J=6.9Hz), 1.43(3H, t, J=6.9Hz), 1.42(3H, t, J=7.3Hz)

[Example 417b]

Synthesis of 2-ethyoxy-3-nitrobenzyl alcohol

[0101] To a mixture of the compound (117 mg) obtained in Example 417a, tetrahydrofuran (5 ml) and methanol (2 ml), lithium borohydride (10.7 mg) was added. The reaction mixture was stirred at room temperature for 15 h, and, after addition of water, concentrated under reduced pressure. To the resulting residue, 2 N HCl was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate=n-hexane = 1 : 2) to give the titled compound quantitatively.

^{1}H-NMR($CDCl_3$)
δ:7.77(1H, d, J=7.9Hz), 7.67(1H, d, J=7.3Hz), 7.22(1H, dd, J=7.9, 7.3Hz), 4.80(2H, s), 4.08(2H, q, J=6.8Hz), 2.10(1H, brs), 1.44(3H, t, J=6.8Hz)

[Example 417c]

Synthesis of 2-ethoxy-3-nitrobenzyl bromide

[0102] To a mixture of the compound (3.13 g) obtained in Example 417b, carbon tetrabromide (5.26 g) and methylene chloride (100 ml), triphenylphosphine (4.16 g) was added under ice cooling. The reaction mixture was stirred under ice cooling for 30 min and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate: n-hexane = 1 : 9) to give 3.59 g of the titled compound (yield, 87%).

^{1}H-NMR ($CDCl_3$)
δ:7.78(1H, dd, J=7.9, 1.7Hz), 7.65(1H, dd, J=7.6, 1.7Hz), 7.20(1H, dd, J=7.9, 7.6Hz), 4.57(2H, s), 4.17(2H, q, J=6.9Hz), 1.49(3H, t, J=6.9Hz)

[Example 417d]

Synthesis of N-(2-ethoxy-3-nitrophenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0103] A mixture of iminodicarboxylic acid di-t-butyl ester (3.23 g), dimethylformamide (50 ml) and sodium hydride (0.57 g) was stirred under ice cooling for 1 h and then a mixture of the compound (3.51 g) obtained in Example 417c and dimethylformamide (20 ml) was added under ice cooling. The reaction mixture was stirred at room temperature for 14 h and, after addition of 2 N HCl, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 9) to give 5.09 g of the titled compound (yield, 95%).

^{1}H-NMR($CDCl_3$)
δ:7.72(1H, dd, J=7.9, 1.3Hz), 7.38(1H, dd, J=7.3, 1.3Hz), 7.17(1H, dd, J=7.9, 7.3Hz), 4.91(2H, s), 4.06(2H, q, J=6.9Hz), 1.45(18H, s), 1.44(3H, t, J=6.9Hz)

[Example 417e]

Synthesis of N-(3-amino-2-ethoxyphenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0104] To a mixture of the compound (5.09 g) obtained in Example 417d, nickel (II) chloride hexahydrate (61 mg) and methanol (130 ml), sodium borohydride (1.46 g) was added. The reaction mixture was stirred at room temperature for 20 min and, after addition of 2 N HCl, adjusted to pH 8 with a saturated aqueous sodium hydrogencarbonate solution and then concentrated under reduced pressure. To the resulting residue, water was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 4) to give the titled compound (yield, 85%).

^{1}H-NMR($CDCl_3$)
δ:6.86(1H, dd, J=7.9, 7.6Hz), 6.63(1H, dd, J=7.6, 1.0Hz), 6.53(1H, dd, J=7.9, 1.0Hz), 4.85(2H, s), 3.90(2H, q, J=6.9Hz), 3.74(2H, brs), 1.43(18H, s), 1.41(3H, t, J=6.9Hz)

Example 500b

Synthesis of N-(5-amino-2-(pyrazole-1-yl)phenylmethyl)carbamic acid t-butyl ester

[Example 500a]

Synthesis of N-(5-nitro-2-(pyrazole-1-yl)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0105] To a mixture of pyrazole (1.0 g) and dimethylsulfoxide (50 ml), sodium hydride(0.54 g) was added under ice cooling. The reaction mixture was stirred under ice cooling for 1 h and then a solution of N-(2-fluoro-5-nitrophenylmethyl)iminodicarboxylic acid di-t-butyl ester (5.0 g) in dimethyl sulfoxide (50 ml) was added. The reaction mixture was stirred at room temperature for 15 h and, after addition of water, subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 4) to give the titled compound (yield, 73%).

^{1}H-NMR($CDCl_3$)
δ:8.22-8.19(2H, m), 7.79-7.78(2H, m), 7.50(1H, d, J=9.6Hz), 6.53(1H, dd, J=2.3, 2.0Hz), 4.95(2H, s), 1.46(18H, s)

[Example 500b]

Synthesis of N-(5-amino-2-(pyrazole-1-yl)phenylmethyl)carbamic acid t-butyl ester

[0106] To a mixture of the compound (4.15 g) obtained in Example 500a, nickel (II) chloride hexahydrate (0.183 g) and methanol (300 ml), sodium borohydride (2.43 g) was added. The reaction mixture was stirred at room temperature for 55 min; thereafter, 2 N HCl was added to render the reaction solution acidic and then a saturated aqueous sodium

hydrogencarbonate solution was added to render the reaction solution basic; subsequently, the reaction mixture was concentrated under reduced pressure. To the resulting residue, water was added and the resulting mixture was subjected to extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was recrystallized from ethyl acetate/n-hexane to give the titled compound (yield, 89%).

^{1}H-NMR($CDCl_3$)
δ:7.69(1H, d, J=1.3Hz), 7.57(1H, d, J=2.0Hz), 7.06(1H, d, J=8.3Hz), 6.86-6.83(1H, m), 6.60(1H, dd, J=8.3, 2.3Hz), 6.41(1H, dd, J=2.0, 1.3Hz), 5.62(1H, brs), 4.01(2H, d, J=6.6Hz), 3.82(2H, brs), 1.43(9H, s)

Example 519e

Synthesis of 3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxyaniline

[Example 519a]

Synthesis of 5-bromo-4-chloro-2-fluoronitrobenzene

[0107] To a mixture of 4-chloro-2-fluoronitrobenzene (1.00 g), silver sulfate (1.95 g) and concentrated sulfuric acid (5 ml), bromine (0.32 ml) was added under ice cooling and the resulting mixture was stirred at 0°C for 30 min, then at room temperature for 1 h. The reaction mixture was put into ice water and subjected to extraction with ether. The organic layer was washed with water, a saturated aqueous sodium hydrogencarbonate solution and a saturated aqueous sodium chloride solution sequentially, dried with anhydrous sodium sulfate and concentrated under reduced pressure to give 1.38 g of the titled compound (yield, 95%).

^{1}H-NMR($CDCl_3$)
δ:7.47(1H, d, J=9.9Hz), 8.37(1H, d, J=7.3Hz)

[Example 519b]

Synthesis of 5-bromo-4-chloro-2-fluoro-3-(trifluoromethylcarbonylaminomethyl)nitrobenzene

[0108] A mixture of the compound (204 mg) obtained in Example 519a, N-hydroxymethyl-2,2,2-trifluoroacetamide (115 mg) and 10% fuming sulfuric acid (1.6 ml) was stirred at 80°C for 10 h. The reaction mixture was cooled, put into ice water and subjected to extraction with ether. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure.

[0109] The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 3) to give 85.1 mg of the titled compound (yield, 28%).

^{1}H-NMR($CDCl_3$)
δ:4.86(2H, d, J=4.0Hz), 6.73(1H, brt), 8.39(1H, d, J=7.3Hz)

[Example 519c]

Synthesis of 5-bromo-3-(t-butoxycarbonylaminomethyl)-4-chloro-2-fluoronitrobenzene

[0110] A mixture of the compound (601 mg) obtained in Example 519b, concentrated sulfuric acid (3 ml) and methanol (12 ml) was heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure and, after being rendered basic by addition of a 2 N aqueous sodium hydroxide solution, it was subjected to extraction with methylene chloride (20 ml). To the organic layer, di-t-butyl dicarbonate (414 mg) and a 2 N aqueous sodium hydroxide solution (10 ml) were added at room temperature and the resulting mixture was stirred at room temperature for 2 h. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, chloroform) to give 402 mg of the titled compound (yield, 66%).

^{1}H-NMR($CDCl_3$)
δ:1.44(9H, s), 4.57-4.66(2H, m), 5.01(1H, brt), 8.31(1H, d, J=7.6Hz)

[Example 519d]

Synthesis of 5-bromo-3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxynitrobenzene

[0111] To a mixture of the compound (200 mg) obtained in Example 519c, ethanol (36 µl) and tetrahydrofuran (5 ml), sodium hydride (content, 60%; 25 mg) was added under ice cooling. The reaction mixture was stirred at 0°C for 2 h and then water and ether were added. The organic layer was washed with water and a saturated aqueous sodium chloride solution sequentially, then dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 1 : 4) to give 197 mg of the titled compound (yield, 92%).

^{1}H-NMR($CDCl_3$)
δ:1.45(9H, s), 1.47(3H, t, J=6.9Hz), 4.08(2H, q, J=6.9Hz), 4.62(2H, d, J=5.9Hz), 4.93(1H, brt), 8.10(1H, s)

[Example 519e]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-4-chloro-2-ethoxyaniline

[0112] Using the compound obtained in Example 519d as a starting material, the procedure of Example 3 was repeated to give the titled compound (86%).

^{1}H-NMR($DCDl_3$)
δ:1.44(3H, t, J=7.3Hz), 1.45(9H, s), 3.78(2H, brs), 3.92(2H, q, J=7.3Hz), 4.47(2H, d, J=5.3Hz), 4.91(1H, brt), 6.63(1H, d, J=8.3Hz), 6.94(1H, d, J=8.3Hz)

Example 520d

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-6-methylaniline

[Example 520a]

Synthesis of 3-methyl-6-nitro-2-(trifluoromethylcarbonylaminomethyl)phenol

[0113] Using 5-methyl-2-nitrophenol as a starting material, the procedure of Example 545b was repeated to give the titled compound (16%).

^{1}H-NMR($CDCl_3$)
δ:2.57(3H, s), 4.67(2H, d, J=6.3Hz), 6.89(1H, d, J=8.6Hz), 7.00(1H, brs), 8.00(1H, d, J=8.6Hz), 11.23(1H, s)

[Example 520b]

Synthesis of 2-(t-butoxycarbonylaminomethyl)-4-methyl-6-nitrophenol

[0114] A mixture of the compound (100 mg) obtained in Example 520a, potassium carbonate (99.4 mg), water (1.0 ml) and methanol (6.0 ml) was stirred at room temperature for 3 h and then di-t-butyl dicarbonate (157 mg) was added. The reaction mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. To the resulting residue, a saturated aqueous sodium chloride solution was added and the mixture was subjected to extraction with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 3 : 17) to give the titled compound (yield, 70%).

^{1}H-NMR($CDCl_3$)
δ:1.43(9H,s), 2.55(3H, s), 4.44(2H, d, J=6.3Hz), 5.17(1H, brs), 6.82(1H, d, J=8.6Hz), 7.94(1H, d, J=8.6Hz), 11.11(1H, s)

[Example 520c]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-4-methylnitrobenzene

[0115] A mixture of the compound (350 mg) obtained in Example 520b, cesium carbonate (404 mg), dimethylformamide (15 ml) and ethyl iodide (0.4 ml) was stirred at 60°C for 2 h. To the reaction mixture, ethyl acetate and water were added. The organic layer was washed with a saturated aqueous sodium chloride solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent, ethyl acetate:n-hexane = 2 : 8) to give the titled compound quantitatively.

^{1}H-NMR($CDCl_3$)
δ:1.44(9H, s), 1.48(3H, t, J=6.9Hz), 2.49(3H, s), 4.03(2H, q, J=6.9Hz), 4.41(2H, d, J=5.6Hz), 4.86(1H, brs), 7.03(1H, d, J=8.6Hz), 7.72(1H, d, J=8.6Hz)

[Example 520d]

Synthesis of 3-(t-butoxycarbonylaminomethyl)-2-ethoxy-4-methylaniline

[0116] Using the compound obtained in Example 520c as a starting material, the procedure of Example 3 was repeated to give the titled compound (92%).

^{1}H-NMR($CDCl_3$)
δ:1.43(3H, t, J=6.9Hz), 1.44(9H, s), 2.26(3H, s), 3.61(2H, brs), 3.89(2H, q, J=6.9Hz), 4.34(2H, d, J=5.3Hz), 4.70(1H, brs), 6.61(1H, d, J=7.9Hz), 6.75(1H, d, J=7.9Hz)

Example 538e

Synthesis of N-(3-amino-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[Example 538a]

Synthesis of 3-nitro-2-(n-propoxy)benzoic acid n-propyl ester

[0117] Using 3-nitrosalicylic acid as a starting material and also using n-propyl iodide as a reagent, the procedure of Example 417a was repeated to give the titled compound (yield, 29%).

^{1}H-NMR($CDCl_3$)
δ:7.98(1H, dd, J=7.6, 1.7Hz), 7,87(1H, dd, J=7.9, 1.7Hz), 7.24(1H, dd, J=7.9, 7.6Hz), 4.31(2H, t, J=6.9Hz), 4.05(2H, t, J=6.9Hz), 1.90-1.71(4H, m), 1.08-0.97(6H, m)

[Example 538b]

Synthesis of 3-nitro-2-(n-propoxy)benzyl alcohol

[0118] Using the compound obtained in Example 538a as a starting material, the procedure of Example 417b was repeated to give the titled compound (yield, 70%).

^{1}H-NMR($CDCl_3$)
δ:7.76(1H, dd, J=8.3, 1.3Hz), 7.68(1H, dd, J=7.3, 1.3Hz), 7.21(1H, dd, J=8.3, 7.3Hz), 4.80(2H, s), 3.96(2H, t, J=6.9Hz), 2.13(1H, brs), 1.91-1.77(2H, m), 1.04(3H, t, J=7.3Hz)

[Example 538c]

Synthesis of 3-nitro-2-(n-propoxy)benzyl bromide

[0119] Using the compound obtained in Example 538b as a starting material, the procedure of Example 417c was repeated to give the titled compound (yield, 95%).

^{1}H-NMR($CDCl_3$)
δ:7.77(1H, dd, J=7.9, 1.3Hz), 7.64(1H, dd, J=7.9, 1.3Hz), 7.19(1H, dd, J=7.9, 7.9Hz), 4.57(2H s), 4.05(2H, t, J=6.6Hz), 1.96-1.83(2H, m), 1.07(3H, t, J=7.3Hz)

[Example 538d]

Synthesis of N-(3-nitro-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0120] Using the compound obtained in Example 538c as a starting material, the procedure of Example 417d was repeated to give the titled compound (yield, 62%).

^{1}H-NMR($CDCl_3$)
δ:7.70(1H, dd, J=7.9, 1.3Hz), 7.37(1H, dd, J=7.9, 1.3Hz), 7.16(1H, dd, J=7.9, 7.9Hz), 4.91(2H, s), 3.94(2H, t, J=6.6Hz), 1.91-1,80(2H, m), 1.45(18H, s), 1.05(3H, t, J=7.3Hz)

[Example 538e]

Synthesis of N-(3-amino-2-(n-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0121] Using the compound obtained in Example 538d as a starting material, the procedure of Example 417e was repeated to give the titled compound quantitatively.

^{1}H-NMR($CDCl_3$)
δ:6.86(1H, dd, J=7.9, 7.6Hz), 6.63(1H, d, J=7.9Hz), 6.52(1H, d, J=7.6Hz), 4.85(2H, s), 3.78(2H, t, J=6.6Hz), 3.74(2H, brs), 1.89-1.75(2H, m), 1.43(18H, s), 1.07(3H, t, J=7.3Hz)

Example 542a

Synthesis of N-(3-amino-2-(i-propoxy)phenylmethyl)iminodicarboxylic acid di-t-butyl ester

[0122] Using 3-nitrosalicylic acid as a staring material and also using i-propyl iodide as a reagent, the procedures of Examples 417a-417e were repeated to give the titled compound.

^{1}H-NMR($CDCl_3$)
δ:6.85(1H, dd, J=7.9, 7.6Hz), 6.62(1H, d, J=7.6Hz), 6.53(1H, d, J=7.9Hz), 4.83(2H, s), 4.26-4.15(1H, m), 3.69(2H, brs), 1.42 (18H, s), 1.31(6H, d, J=6.3Hz)

Test Examples

Test Example 1

[0123] Compounds of the invention were evaluated for their inhibitory effect on the presently known three NOS isoforms.

[0124] Crude enzymes of the respective NOS isoforms were prepared by the following procedures (Nagafuji et al., Neuroreport 6, 1541 - 1545, 1995).

[0125] The crude enzyme of nNOS was prepared by the following procedure. Normal untreated male Sprague Dawley (SD) rats (body weight, 300 - 400 g) were decapitated; the whole brain was immediately taken out from each animal and the cerebral cortex was separated on ice. Then, 5 volumes of 50 mM Tris-HCl containing 1 mM DTT (pH 7.4) was added and the mixture was homogenized for 3 min and centrifuged at 1,000 x g for 10 min. The resulting supernatant was further centrifuged at 100,000 x g for 60 min and a soluble cytosolic fraction of the finally obtained supernatant was used as the crude enzyme of nNOS.

[0126] The crude enzyme of iNOS was prepared by the following procedure. Rats were administered LPS (10 mg/kg) intraperitoneally and, 6 h later, perfused in a transcardiac manner with physiological saline containing 10 U/ml of heparin; thereafter, lungs were taken out. Subsequently, 5 volumes of 50 mM Tris-HCl containing 1 mM DTT (pH 7.4) was added and the mixture was homogenized for 3 min, followed by centrifugation of the homogenate at 1,000 x g for 10 min. The resulting supernatant was centrifuged at 100,000 x g for 60 min and a soluble cytosolic fraction of the finally obtained supernatant was used as the crude enzyme of iNOS.

[0127] The crude enzyme of eNOS was prepared by the following procedure. Cow pulmonary arterial endothelium

cells (CPAE) were cultured in a MEM medium containing 20% FBS. Several days later, the cells were detached from the flask using a 0.25% trypsin solution containing 1 mM EDTA and, after addition of a suitable amount of FBS, centrifuged at 1,000 rpm for 10 min. A suitable amount of Ca- and Mg-free phosphate buffer (pH 7.4) was added to the precipitating cells and they were centrifuged at 1,000 rpm for 10 min. The same step was repeated to wash the cells which, upon addition of 50 mM Tris-HCl (pH 7.4) containing 1% Triton X-100 and 1 mM DTT, were left to stand in ice for 1 h. Subsequently, the mixture was homogenized for 3 min and kept in ice for 30 min with occasional stirring. Finally, the mixture was centrifuged at 100,000 x g for 60 min and the resulting supernatant was used as the crude enzyme of eNOS.

[0128] The method of measuring NOS activity was basically the same as already reported by the present inventors and consisted of determining quantitatively the conversion of a substrate L-[^{3}H]arginine to a reaction product L-[^{3}H] citrulline (Nagafuji et al., in Brain Edema IX (Ito et al, eds.) 60, pp. 285 - 288, 1994; Nagafuji et al., Neuroreport 6, 1541 - 1545, 1995)

[0129] The reaction solution consisted of 100 nM L-[^{3}H] arginine, a prepared crude NOS enzyme sample (10 - 30 μg/ml protein), 1.25 mM $CaCl_2$, 1 mM EDTA, 10 μg/ml calmodulin, 1 mM NADPH, 100 μM tetrahydrobiopterine, 10 μM FAD, 10 μM FMN and 50 mM Tris-HCl (pH 7.4), to which one of the compounds of the invention or one of the control compounds was added.

[0130] The reaction was started by addition of L-[^{3}H] arginine. After incubation at 37°C for 10 min, the reaction was terminated by addition of 2 ml of 50 mM Tris-HCl (pH 5.5) containing 1 mM EDTA and placing the mixture on ice. The reaction solution was passed through a cation-exchange resin column (Dowex AG50WX-8, Na^+ form, 3.2 ml) to separate the reaction product L-[^{3}H] citrulline from the unreacted residual substrate L-[^{3}H] arginine. The eluate was combined with another eluate resulting from the passage of a given amount of distilled water through the column and put into a minivial for recovery of L-[^{3}H] citrulline. Thereafter, a scintillation fluid was added and the contained radioactivity was measured with a liquid scintillation counter to determine the amount of L-[^{3}H] citrulline.

[0131] The activity of nNOS or eNOS was determined by subtracting the activity detected in the absence of $CaCl_2$ and calmodulin from the activity detected in the presence of $CaCl_2$ and calmodulin. The activity of iNOS was detected in the absence of $CaCl_2$ and calmodulin. The protein concentration of each crude enzyme sample was determined with a micro-assay kit of Bio Rad Co. Each Experiment was conducted in a duplicate.

[0132] Table 81 lists the mean values of IC_{50} (the concentration necessary to inhibit 50% activity) of all test compounds against each NOS isoform. The table also lists the ratios of IC_{50} values to each other as an index of selectivity.

Table 81

Inhibitory Action and Selectivity of Test Compounds against Three NOS Isoforms						
Example No. or Control Compound	Inhibitory action			Selectivity		
	nNOS	IC_{50}(nM) iNOS	eNOS	iNOS/nNOS	eNOS/nNOS	eNOS/iNOS
18	22.6	916.7	322.4	41	14	0.14
52	79.8	N.D.	1476.7	-	19	-
53	86.1	N.D.	6624.3	-	77	-
57	70.8	N.D.	947.4	-	13	-
61	126.0	N.D.	1614.9	-	13	
151	126.2	N.D.	679.3	-	5	-
153	29.8	N.D.	586.1	-	20	-
458	20.8	N.D.	403.1	-	19	-
460	111.7	N.D.	1244.3	-	11	-
462	16.4	N.D.	257.2	-	16	-
465	31.2	N.D.	1000.0	-	32	-
466	35.5	N.D.	421.0	-	12	-
467	19.6	N.D.	274.6	-	14	-
468	56.3	N.D.	2481.0	-	44	-

Table 81 (continued)

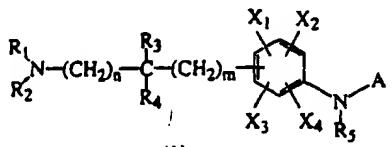
Inhibitory Action and Selectivity of Test Compounds against Three NOS Isoforms						
Example No. or Control Compound	Inhibitory action			Selectivity		
	nNOS	IC_{50}(nM) iNOS	eNOS	iNOS/nNOS	eNOS/nNOS	eNOS/iNOS
469	40.0	N.D.	994.0	-	25	-
478	61.6	N.D.	447.5	-	7	-
479	66.9	N.D.	802.0	-	12	-
481	78.1	N.D.	1984.5	-	25	-
482	50.5	N.D.	1348.6	-	27	-
483	65.4	N.D.	711.0	-	11	-
484	69.2	N.D.	1264.2	-	18	-
485	54.4	1774.9	2882.4	32	53	1.6
488	39.9	N.D.	297.9	-	8	-
489	22.1	N.D.	N.D.	-	-	-
490	18.1	N.D.	347.5	-	19	-
491	45.8	N.D.	1768.0	-	39	-
506	29.1	N.D.	1292.7	-	45	-
521	19.5	N.D.	485.2	-	25	-
522	19.7	N.D.	398.4	-	20	-
541	25.9	N.D.	712.6	-	28	-
543	12.5	N.D.	249.8	-	20	-
L-NA	16.9	3464.3	68.2	205.0	4.0	0.02
Notes: Symbol "N.D." means "not determined", and "-" means "uncalculable"						

INDUSTRIAL APPLICABILITY

[0133] The compounds of the present invention exhibit an outstanding nNOS or iNOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

Claims

1. A compound represented by the general formula (I), or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof:



(I)

(where R_1 and R_2 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxycarbonyl group, or R_1 and R_2 may combine together to form a 3- to 8-membered ring;

R_3 and R_4 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms;
R_5 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;
X_1, X_2, X_3, and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl, group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=O)X_7$;
where X_5 and X_6 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring;
X_7 is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX_8X_9;
where X_8 and X_9 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_8 and X_9 may combine together to form a 3- to 8-membered ring;
A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;
n and m are each an integer of 0 or 1).

2. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

X_1, X_2, X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=O)X_7$; and
A is an optionally substituted benzene or pyridine ring.

3. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

A is a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom (exclusive of an optionally substituted pyridine ring).

4. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optionally active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1 is a hydrogen atom;
R_2 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group; and
A is an optionally substituted benzene ring.

5. The compound of the general formula (1) according to claim 2 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

A is an optionally substituted pyridine ring.

6. The compound of the general formula (1) according to claim 1 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1 and R_2 are each a hydrogen atom;
R_5 is a hydrogen atom;
X_1, X_2, X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group or NX_5X_6; and
A is an optionally substituted benzene ring, an optionally substituted pyridine ring, an optionally substituted pyrimidine ring, an optionally substituted oxazole ring, or an optionally substituted thiazole ring.

7. The compound of the general formula (1) according to claim 6 or a possible tautomer, stereoisomer or optionally active form of the compound or a pharmaceutically acceptable salt thereof, in which:

A is an optionally substituted benzene ring or an optionally substituted pyridine ring.

8. The compound of the general formula (1) according to any one of claims 1 - 7 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_3 and R_4 which may be the same or different are each a hydrogen atom or a lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic ring having 3 - 10 carbon atoms.

9. The compound of the general formula (1) according to any one of claims 1 - 8 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

X_1, X_2, X_3 and X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group optionally substituted by a phenyl group or NX_5X_6;
where X_5 and X_6 which may be the same or different are each a hydrogen atom, a lower alkyl group optionally substituted by a phenyl group or an acyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring.

10. The compound of the general formula (1) according to claim 6, 8 or 9 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which A is an optionally substituted benzene ring or an optionally substituted pyridine ring, with the optional substituent being a nitro group, a lower alkoxy group, a lower alkyl group or a lower alkylthio group.

11. The compound of the general formula (1) according to any one of claims 1 - 8 or claim 10 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

X_1, X_2, X_3, or X_4 which may be the same or different are each a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxy group or NX_5X_6;
where X_5 and X_6 which may be the same or different are each a hydrogen atom, a lower alkyl group or an acyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring.

12. The compound of the general formula (1) according to any one of claims 1 - 11 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

m and n are each 0; and
the substituents other than X_1, X_2, X_3, and X_4 are meta-substituted on the benzene ring.

13. The compound of the general formula (1) according to any one of claims 1 - 11 or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

m + n = 1 ; and
the substituents other than X_1, X_2, X_3 and X_4 are ortho- or para-substituted on the benzene ring.

14. The compound of the general formula (1) according to claim 1 or a pharmaceutically acceptable salt thereof, said compound being selected from the group consisting of:

2-(3-aminomethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-ethyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-ethoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitrobenzene, 2-(3-aminomethylphenylamino)-6-methoxy-3-nitrobenzene,
2-(3-aminomethyl-2-methylphenylamino)-6-methoxy-3-nitropyridine,
2-(4-aminoethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-fluorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-

methylethyl)-phenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethoxyphenylamino)-4-methylpyridine,

2-(2-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-chlorophenylamino)-4-methylpyridine, 2-(3-(1-amino-cyclobutyl)phenylamino)-4-methylpyridine, 2-(4-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chlorophenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-(n-propoxy)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chloro-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-4-methylpyridine, and 2-(3-aminomethyl-2-(i-propoxy)phenylamino)-4-methylpyridine.

15. A nNOS inhibitor containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

16. A therapeutic of cerebrovascular diseases containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

17. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral hemorrhage.

18. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is subarachnoid hemorrhage.

19. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral infarction.

20. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is atherothrombotic infarction.

21. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is lacunar infarction.

22. The therapeutic according to claim 19, wherein the subtype of cerebral infarction is cardiogenic embolism.

23. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is transient ischemic attack.

24. The therapeutic according to claim 16, wherein the type of cerebrovascular diseases is cerebral edema.

25. A therapeutic of traumatic brain injury containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

26. A therapeutic of spinal injury containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

27. An analgesic containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

28. The therapeutic according to claim 27, wherein the type of pain is headache.

29. The therapeutic according to claim 28, wherein the subtype of headache is migraine.

30. The therapeutic according to claim 28, wherein the subtype of headache is tension headache.

31. The therapeutic according to claim 28, wherein the subtype of headache is cluster headache or chronic paroxysmal headache.

32. A therapeutic of Parkinson's disease containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

33. A therapeutic of Alzheimer's disease containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

34. A therapeutic of seizure containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

35. A therapeutic effective against morphine tolerance or dependence containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

36. A therapeutic of septic shock containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

37. A therapeutic of chronic rheumatoid arthritis containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

38. A therapeutic of osteoarthritis containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

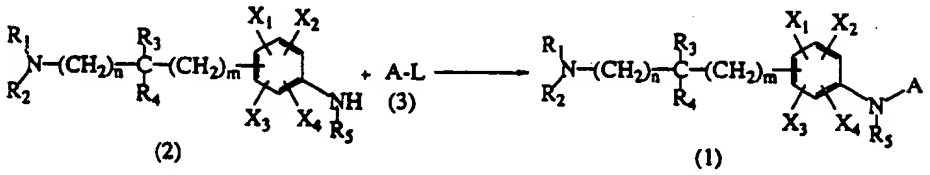
39. A therapeutic of viral or nonviral infections containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

40. A therapeutic of diabetes mellitus containing as an active ingredient a compound represented by the general formula (1) or a possible tautomer, stereoisomer or optically active form of the compound or a pharmaceutically acceptable salt thereof, in which:

R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1.

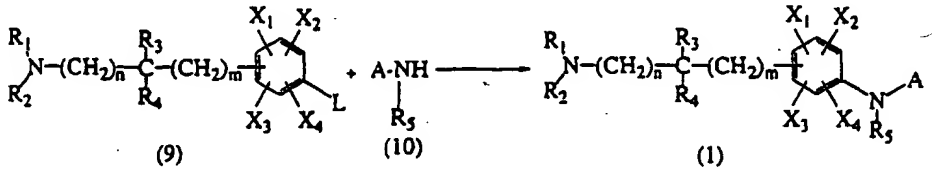
41. A process for producing a compound according to claim 1 by the reaction pathway (A):
Reaction pathway (A)



provided that in the general formula (1), (2) or (3),

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1;
R_3 is a hydrogen atom or an optionally substituted lower alkyl group; and
L is a leaving group.

42. A process for producing a compound according to claim 1 by the reaction pathway (B):
Reaction pathway (B)



provided that in the general formula (1), (9) or (10),

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, n, m and A have the same meanings as defined in claim 1;
R_5 is a hydrogen atom or an optionally substituted lower alkyl group; and
L is a leaving group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07C211/54, C07C211/56, C07C209/10, C07D239/42, C07D241/20, C07D263/48, C07D207/335, C07D207/337, C07D401/12, C07D205/04,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07C1/00-409/44, C07D201/00-521/00, A61K6/00-49/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 5362747, A (ABBOTT LAB.), November 8, 1994 (08. 11. 94) (Family: none)	1-42
A	WO, 94/12163, A1 (ABBOTT LAB.), June 9, 1994 (09. 06. 94) (Family: none)	1-42
X	JP, 8-501096, A (Merrell Dow Pharmaceuticals Inc.), February 6, 1996 (06. 02. 96)	1, 32
A	& EP, 585500, A1 & WO, 94/05648, A1 & AU, 668413, B & EP, 658157, A1	2-31, 33-42
X	WO, 94/25448, A1 (YAMANOUCHI PHARM. CO. LTD.), November 10, 1994 (10. 11. 94)	1, 40
A	& EP, 696585, A1 & US, 5643931, A	2-39, 41, 42
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A	iminodibenzyl", Eur. J. Med. Chem. - Chim. Ther. (1977) 12(3) p.219-225	2-33, 35-42

[x] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
March 30, 1998 (30. 03. 98)	April 21, 1998 (21. 04. 98)
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Facsimile No.	Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	p.1208-1213	2-23, 25-37, 39-42
X	JP, 5-186431, A (Elf Sanofi), July 27, 1993 (27. 07. 93)	1, 40
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X	WO, 96/36620, A1 (SMITHKLINE BEECHAM SPA), November 21, 1996 (21. 11. 96)	1
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A	& WO, 95/12572, A1 & EP, 677039, A1	2-42
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A		2-42
X	JP, 5-221989, A (Imperial Chemical Industries PLC.),	1
A	August 31, 1993 (31. 08. 93) & EP, 539066, A1 & CA, 2079414, A1 & US, 5373015, A	2-42
X	JP, 5-58998, A (Taisho Pharmaceutical Co., Ltd.), March 9, 1993 (09. 03. 93) (Family: none)	1
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IL'INA, I.G. et al., "Synthesis and chiroptical properties of electron acceptors of the picryl	1
A	series", Zh. Org. Khim., (1985) 21(12) p.2529-2532	2-42
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A	Trans. 1(1972) (3) p.353-355	2-42
X	GALE, David M. "Fluoroalkylamines", J. Org. Chem., (1968) 33(3) p.1002-1008	1
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X	Chem. Abstr., (1958) Vol. 52, No. 21, 10 November 1958 (Columbus, OH, USA), the abstract No. 18318d,	1
A	STERLING, J.D. et al., "Derivatives of 4-anilino-3-nitrobenzenesulfonamide", US, 2834794, A (13 May 1958)	2-42
X	Chem. Abstr., (1957) Vol. 51, No. 4, 25 February 1957 (Columbus, OH, USA), the abstract No. 2881i-2882b,	1
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP97/04762

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

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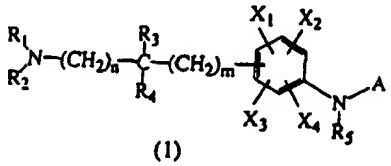
(54) AROMATIC AMINE DERIVATIVES HAVING NOS INHIBITORY EFFECT

(57) Compounds represented by the general formula (1):



(1)

(where R_1 and R_2 are typically a hydrogen atom; R_3 and R_4 are typically a hydrogen atom or a lower alkyl group; R_5 is typically a hydrogen atom; X_1, X_2, X_3 and X_4 are typically a hydrogen atom or a lower alkoxy group; A is typically an optionally substituted pyridine ring; m and n are each 0 or 1) have an NOS inhibiting activity and are useful as therapeutics of cerebrovascular diseases and other pharmaceuticals.

EP 0 949 242 A1

Description

TECHNICAL FIELD

[0001] This invention relates to N-substituted aniline derivatives, more particularly to compounds represented by the general formula (I) that have a nitric oxide synthase (NOS) inhibiting action to suppress the production of nitric oxide (NO) and thereby prove effective against disorders and diseases in which excessive NO or NO metabolites are supposedly involved, namely, cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothromobotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus. The invention also relates to possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof. The invention further relates to preventives and therapeutics that contain said compounds, derivatives or pharmaceutically acceptable salts as active ingredients.

BACKGROUND ART

[0002] The number of deaths from cerebrovascular diseases in Japan had increased until 1970 when it began to decline mostly due to the improvement in their acute-phase therapy. Nevertheless, cerebrovascular diseases remain the second leading cause of death among adult diseases, next only to cancers. As for the incidence of cerebrovascular diseases, many statistical surveys indicate that it is generally constant and in view of the fact that the number of elderly persons will increase at an uncomparably faster speed in Japan than any other country in the world, the number of patients suffering from cerebrovascular diseases is estimated to increase rather than decrease in the future. The declining mortality and the growing population of aged people combine to increase the cases of cerebrovascular diseases in the chronic phase and this has presented with a national problem not only from the aspects of individual patients and society at large but also from the viewpoint of medical economics since patients with chronic cerebrovascular disease are inevitably involved in long-term care. In cerebral infarction that accounts for most cases of cerebrovascular diseases, cerebral arteries are occluded and blood deficit starting at the blocked site extends to the peripheral site, causing an ischemic state. The symptoms of cerebral infarction in the chronic phase are in almost all cases derived from the loss of neurons and it would be extremely difficult to develop medications or established therapeutic methods for achieving complete recovery from those symptoms. Therefore, it is no exaggeration that the improvement in the performance of treatments for cerebral infarction depends on how patients in an acute phase can be treated with a specific view to protecting neurons and how far their symptoms can be ameliorated in the acute phase. However, most of the medications currently in clinical use are antiplatelet drugs, anticoagulants and thrombolytics and none of these have a direct nerve protecting action (see Kazuo MINEMATSU et al., "MEDICINA", published by Igaku Shoin, 32, 1995 and Hidehiro MIZUSAWA et al., published by Nankodo, "Naika" 79, 1997). Therefore, it is desired to develop a drug that provides an effective therapy for cerebrovascular diseases, in particular cerebral infarction, by working in an entirely novel and different mechanism of action from the conventional medications.

[0003] A presently dominant theory based on genetic DNA analyses holds that NOS exists in at least three isoforms, namely, calcium-dependent nNOS (type 1) which is present constitutively in neurons, calcium-dependent eNOS (type 3) which is present constitutively in vascular endothelial cells, and apparently calcium-independent iNOS (type 2) which is induced and synthesized by stimulation with cytokines and/or lipopolysaccharides (LPS) in macrophages and many other cells (Nathan et al., FASEB J. 16, 3051-3064, 1992; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0004] A mechanism that has been proposed as being most probable for explaining the brain tissue damage which accompanies cerebral ischemia is a pathway comprising the sequence of elevation in the extracellular glutamic acid level, hyperactivation of glutamic acid receptors on the post-synapses, elevation in the intracellular calcium level and activation of calcium-dependent enzymes (Siesjö, J. Cereb. Blood Flow Metab. 1, 155-185, 1981; Siesjö, J. Neurosurg. 60, 883-908, 1984; Choi, Trends Neurosci. 11, 465-469, 1988; Siesjö and Bengstsson, J. Cereb. Blood Flow Metab. 9, 127-140, 1989). As already mentioned, nNOS is calcium-dependent, so the inhibition of hyperactivation of this type of NOS isoforms would contribute to the neuro-protective effects of NOS inhibitors (Dawson et al., Annals Neurol. 32, 297-311, 1992).

[0005] As a matter of fact, the mRNA level of nNOS and the number of nNOS containing neurons start to increase early after focal cerebral ischemia in rats and their temporal alterations coincide with the development of infarction (Zhang et al., Brain Res. 654, 85-95, 1994). In addition, in a mouse model of focal cerebral ischemia, the percent inhibition of nNOS activity and the percent reduction of infarct volume correlate to each other at least in a dose range of N^G-nitro-L-arginine (L-NA) that produces a recognizable infarct volume reductive action (Carreau et al., Eur. J. Pharmacol. 256, 241-249, 1994). Further in addition, it has been reported that in nNOS knockout mice, the infarct volume

observed after focal cerebral ischemia is significantly smaller than that in the control (Huang et al., Science 265, 1883-1085, 1994).

[0006] Referring now to NO, it is at least one of the essences of endothelium-derived relaxing factor (EDRF) and, hence, is believed to take part in the adjustment of the tension of blood vessels and the blood flow (Moncade et al., Pharmacol. Rev. 43, 109-142, 1991). As a matter of fact, it was reported that when rats were administered high doses of L-NA, the cerebral blood flow was found to decrease in a dose-dependent manner as the blood pressure increased (Toru MATSUI et al., Jikken Igaku, 11, 55-60, 1993). The brain has a mechanism by which the cerebral blood flow is maintained at a constant level notwithstanding the variations of blood pressure over a specified range (which is commonly referred to as "autoregulation mechanism") ("NOSOTCHU JIKKEN HANDBOOK", complied by Keiji SANO, published by IPC, 247-249, 1990). The report of Matsui et al. suggests the failure of this "autoregulation mechanism" to operate. Therefore, if eNOS is particularly inhibited beyond a certain limit in an episode of brain ischemia, the cerebral blood flow will decrease and the blood pressure will increase, thereby aggravating the dynamics of microcirculation, possibly leading to an expansion of the ischemic lesion. It was also reported that in eNOS knockout mice, the infarct observed after focal cerebral ischemia was larger than that in the control but could be reduced significantly by administration of L-NA (Huang et al., J. Cereb. Blood Flow Metab. 16, 981-987, 1996). These reports show that eNOS-derived NO probably works protectively on the brain tissue through the intermediary of a vasodilating action, a platelet aggregation suppressing action and so forth.

[0007] The present inventors previously found that L-NA, already known to be a NOS inhibitor, possessed ameliorative effects on the brain edema and cerebral infarction following phenomena that developed after experimental cerebral ischemia (Nagafuji et al., Neurosci. Lett. 147, 159-162, 1992; Japanese Patent Public Disclosure No. 192080/1994), as well as necrotic neuronal cell death (Nagafuji et al., Eur. J. Pharmacol. Env. Tox. 248, 325-328, 1993). On the other hand, relatively high doses of NOS inhibitors have been reported to be entirely ineffective against ischemic brain damage and sometimes aggravating it (Idadecola et al., J. Cereb. Blood Flow Metab. 14, 175-192, 1994; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995). It should, however, be stressed that as a matter of fact, all papers that reported the changes of NO or NO-related metabolites in the brain and blood in permanent or temporary cerebral ischemic models agreed in their results to show the increase in the levels of those substances (Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku, 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0008] One of the reasons for explaining the fact that conflicting reports have been made about the effectiveness of NOS inhibitors in cerebral ischemic models would be the low selectivity of the employed NOS inhibitors for nNOS. As a matter of fact, no existing NOS inhibitors including L-NA and N^G-nitro-L-arginine methyl ester (L-NAME) have a highly selective inhibitory effect on a specific NOS isoform (Nagafuji et al. Neuroreport 6, 1541-1545, 1995; Nagafuji et al. Mol. Chem. Neuropathol. 26, 107-157, 1995). Therefore, it may well be concluded that desirable therapeutics of ischemic cerebrovascular diseases should have a selective inhibitory effect on nNOS (Nowicki et al., Eur. J. Pharmacol. 204, 339-340, 1991; Dawson et al., Proc. Natl. Acad. Sci. USA 88, 6368-6371, 1991; Iadecola et al., J. Cereb. Blood Flow Metab. 15, 52-59, 1995; Iadecola et al., J. Cereb. Blood Flow Metab. 15, 378-384, 1995; Toshiaki NAGAFUJI and Toru MATSUI, Jikken Igaku 13, 127-135, 1995; Nagafuji et al., Mol. Chem. Neuropathol. 26, 107-157, 1995).

[0009] It has also been suggested that nNOS inhibitors have the potential for use as therapeutics of traumatic brain injuries (Oury et al., J. Biol. Chem. 268, 15394-15398, 1993; MacKenzie et al., Neuroreport 6, 1789-1794, 1995; Mesenge et al., J. Neurotrauma. 13, 11-16, 1996; Wallis et al., Brain Res., 710, 169-177, 1996), headache and other pains (Moore et al., Br. J. Pharmacol. 102, 198-202, 1991; Olesen., Trends Pharmacol. 15, 149-153, 1994), Parkinson's disease (Youdim et al., Advances Neurol. 60, 259-266, 1993; Schulz et al., J. Neurochem. 64, 936-939, 1995; Hantraye et al., Nature Medicine 2, 1017-1021, 1996), Alzheimer's disease (Hu and El-FaKahany, Neuroreport 4, 760-762, 1993 Meda et al., Nature 374, 647-650, 1995), seizure (Rigaud-Monnet et al., J. Cereb. Blood Flow Metab. 14, 581-590, 1994), and morphine tolerance and dependence (Kolesnikov et al., Eur. J. Pharmacol. 221, 399-400, 1992; Cappendijk et al., Neurosci. Lett. 162, 97-100, 1993).

[0010] Upon stimulation by certain kinds of cytokines and/or LPS, iNOS is induced in immunocytes such as macrophages and glial cells and other cells, and the resulting large amount of NO will dilate blood vessels to cause a fatal drop in blood pressure. Therefore, it is speculated that an iNOS inhibitor may be effective against septic shocks (Kilbourn and Griffith, J. Natl. Cancer Inst. 84, 827-831, 1992; Cobb et al., Crit. Care Med. 21, 1261-1263, 1993; Lorente et al., Crit. Care Med. 21, 1287-1295, 1993). Further, it has been suggested that iNOS inhibitors are useful as therapeutics of chronic rheumatoid arthritis and osteoarthritis (Farrell et al., Ann, Rheum. Dis. 51, 1219-1222, 1992; Hauselmann et al., FEBS Lett. 352, 361-364, 1994; Islante et al., Br. J. Pharmacol. 110, 701-706, 1993), viral or nonviral infections (Zembvitz and Vane, Proc. Natl. Acad. Sci. USA 89, 2051-2055, 1992; Koprowski et al., Proc. Natl. Acad. Sci. USA 90, 3024-3027, 1993) and diabetes mellitus (Kolb et al., Life Sci. PL213-PL217, 1991).

[0011] The NOS inhibitors so far reported to have a certain degree of selectivity for nNOS are N^G-cyclopropyl-L-arginine (L-CPA)(Lamberte et al., Eur. J. Pharmacol. 216, 131-134, 1992), L-NA (Furfine et al., Biochem. 32, 8512-8517, 1993), S-methyl-L-thiocitrulline (L-MIN) (Narayanan and Griffith, J. Med. Chem. 37, 885-887, 1994; Furfine et al.,

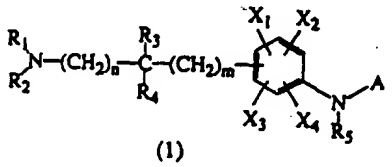
J. Biol. Chem. 37, 885-887, 1994; Furfine et al. J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al., J. Biol. Chem. 270, 11103-11110, 1995; Nagafuji et al., Neuroreport 6, 1541-1545, 1995), S-ethyl-L-thiocitrulline (L-EIN) (Furfine et al., J. Biol. Chem. 269, 26677-26683, 1994; WO95/09619; Narayanan et al.,J. Biol. Chem. 270, 11103-11110, 1995), and ARL 17477 (Gentile et al., WO95/05363; Zhang et al., J. Cereb. Blood Flow Metab., 16, 599-604, 1996).

[0012] In addition, the inhibitors that have been reported to have a certain degree of selectivity for iNOS are N^G-iminoethyl-L-ornithine (L-NIO) (McCall et al., Br. J. Pharmacol. 102, 234-238, 1991) and aminoguanidine (AG) (Griffith et al., Br. J. Pharmacol. 110, 963-968, 1993; Hasan et al. Eur. J. Pharmacol. 249, 101-106, 1993).

DISCLOSURE OF INVENTION

[0013] An object of the present invention is to provide novel compounds that have an inhibitory effect on calcium-dependent nNOS which is present constitutively in the brain, particularly in neurons or an inducible and apparently calcium-independent iNOS and which are useful as therapeutics of cerebrovascular diseases [cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction (atherothrombotic infarction, lacunar infarction and cardiogenic embolism), transient ischemic attack and cerebral edema], traumatic brain injury, spinal injury, pains [headache (migraine, tension headache, cluster headache and chronic paroxysmal headache)], Parkinson's disease, Alzheimer's disease, seizure, morphine tolerance or dependence, septic shock, chronic rheumatoid arthritis, osteoarthritis, viral or nonviral infections and diabetes mellitus.

[0014] As a result of the intensive studies made in order to attain the stated object, the present inventors found that aromatic amine derivatives represented by the general formula (I), or possible tautomers, stereoisomers and optically active forms of said compounds, as well as pharmaceutically acceptable salts thereof have an inhibitory action on type 1 NOS and so forth, thereby exhibiting marked effectiveness as therapeutics of cerebrovascular diseases (especially as therapeutics of occlusive cerebrovascular diseases):



(1)

(where R_1 and R_2 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group or a lower alkoxycarbonyl group, or R_1 and R_2 may combine together to form a 3- to 8-membered ring;

R_3 and R_4 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or R_3 and R_4 may combine together to form a monocyclic or fused ring having 3 - 10 carbon atoms;
R_5 is a hydrogen atom, a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;
X_1, X_2, X_3, and X_4, which may be the same or different are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a hydroxyl group, an optionally substituted lower alkyl group, a lower alkenyl group, a lower alkynyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group, a phenyl group optionally substituted by a halogen atom and/or a lower alkyl group, NX_5X_6 or $C(=O)X_7$;
where X_5 and X_6 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_5 and X_6 may combine together to form a 3- to 8-membered ring;
X_7 is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, or NX_8X_9;
where X_8 and X_9 which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_8 and X_9 may combine together to form a 3- to 8-membered ring;
A is an optionally substituted benzene ring or a 5- or 6-membered aromatic hetero ring which is optionally substituted and which contains at least one nitrogen atom as a hetero atom;
n and m are each an integer of 0 or 1).

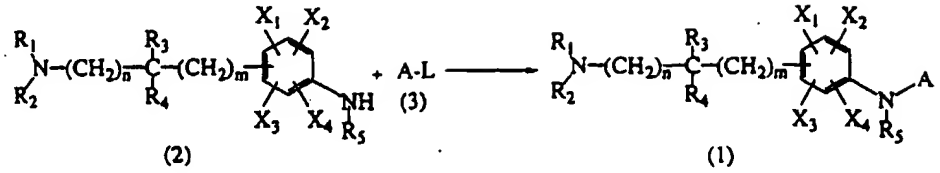
[0015] The present invention has been accomplished on the basis of this finding.

[0016] The present invention also provides a process for producing a compound of the general formula (1) which is

represented by the reaction pathway (A):

Reaction pathway (A)

[0017]



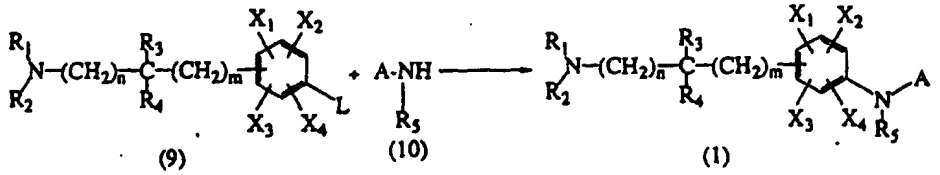
(2) (1)

namely, a process in which a substituted aniline represented by the general formula (2) (where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, n and m have the same meanings as defined above; R_5 is a hydrogen atom or an optionally substituted lower alkyl group) is reacted with a compound represented by the general formula (3) (where A has the same meaning as defined above; L is a leaving group) to produce a compound represented by the general formula (1).

[0018] The present invention further provides a process for producing a compound of the general formula (1) which is represented by the reaction pathway (B):

Reaction pathway (B)

[0019]



(9) (10) (1)

namely, a process in which a substituted benzene represented by the general formula (9) (where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, L, n and m have the same meanings as defined above) is reacted with a compound represented by the general formula (10) (where A and R_5 have the same meanings as defined above) to produce a compound represented by the general formula (1).

BEST MODE FOR CARRYING OUT THE INVENTION

[0020] In the present invention, the 5- or 6-membered aromatic hetero ring as an example of A which contains at least one nitrogen atom as a hetero atom may be exemplified by a pyrrole ring, a pyrrole-1-oxide ring, a pyrazole ring, a pyrazole-1-oxide ring, a pyrazole-2-oxide ring, a pyrazole-1,2-dioxide ring, an imidazole ring, an imidazole-1-oxide ring, an imidazole-3-oxide ring, an imidazole-1,3-dioxide ring, an isoxazole ring, an isoxazole-2-oxide ring, an oxazole ring, an oxazole-3-oxide ring, an isothiazole ring, an isothiazole-1-oxide ring, an isothiazole-1,1-dioxide ring, an isothiazole-1,2-dioxide ring, an isothiazole-2-oxide ring, a thiazole ring, a thiazole-1-oxide ring, a thiazole-1,1-dioxide ring, a thiazole-3-oxide ring, a pyridine ring, a pyridine-N-oxide ring, a pyridazine ring, a pyridazine-1-oxide ring, a pyridazine-1,2-dioxide ring, a pyrimidine ring, a pyrimidine-1-oxide ring, a pyrimidine-1,3-dioxide ring, a pyrazine ring, a pyrazine-1-oxide ring or a pyrazine-1,4-dioxide ring or the like;

the substituent in A is a hydroxyl group, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a lower alkoxy group, a lower alkyl group, a lower alkylthio group, $NX_{10}X_{11}$ or $C(=O)X_{12}$;
where X_{10} and X_{11} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, an acyl group, an optionally substituted lower alkoxycarbonyl group, or X_{10} and X_{11} may combine

together to form a 3- to 8-membered ring;

X_{12} is a hydrogen atom, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group or $NX_{13}X_{14}$;

where X_{13} and X_{14} which may be the same or different are each a hydrogen atom, an optionally substituted lower alkyl group, or X_{13} and X_{14} may combine together to form a 3- to 8-membered ring;

the lower alkyl group is a straight-chained alkyl group having 1 - 6 carbon atoms, or a branched or cyclic alkyl group having 3 - 8 carbon atoms and may be exemplified by a methyl group, an ethyl group, an n-propyl group, an n-butyl group, an n-pentyl group, an n-hexyl group, an i-propyl group, an i-butyl group, a sec-butyl group, a t-butyl group, an i-pentyl group, a neopentyl group, a t-pentyl group, an i-hexyl group, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group or a cyclooctyl group or the like;

the lower alkenyl group is a straight-chained alkenyl group having 2 - 6 carbon atoms or a branched alkenyl group having 3 - 6 carbon atoms and may be exemplified by a vinyl group, an allyl group, a 1-butenyl group, a 1-pentenyl group, a 1-hexenyl group, a 2-butenyl group, a 2-pentenyl group, a 2-hexenyl group, an isopropenyl group, a 2-butenyl group or a 1-methyl-1-propenyl group or the like;

the lower alkynyl group is a straight-chained alkynyl group having 2 - 6 carbon atoms or a branched alkynyl group having 3 - 6 carbon atoms and may be exemplified by an ethynyl group, a 1-propynyl group, a 1-butynyl group, a 1-pentynyl group, a 1-hexynyl group, a 2-propynyl group, a 2-butynyl group, a 2-pentynyl group, a 2-hexynyl group, a 1-methyl-2-propynyl group, a 3-methyl-1-butynyl group or a 1-ethyl-2-propynyl group or the like;

the lower alkoxy group is a straight-chained alkoxy group having 1 - 6 carbon atoms or a branched or cyclic alkoxy group having 3 - 8 carbon atoms and may be exemplified by a methoxy group, an ethoxy group, an n-propoxy group, an n-butoxy group, an n-pentoxy group, an n-hexoxy group, an i-propoxy group, an i-butoxy group, a sec-butoxy group, a t-butoxy group, an i-pentoxy group, a neopentoxy group, a t-pentoxy group, an i-hexoxy group, a cyclopropoxy group, a cyclobutoxy group, a cyclopentoxy group, a cyclohexoxy group, a cycloheptoxy group or a cyclooctoxy group or the like;

the lower alkylthio group is a straight-chained alkylthio group having 1 - 6 carbon atoms or a branched or cyclic alkylthio group having 3 - 8 carbon atoms and may be exemplified by a methylthio group, an ethylthio group, an n-propylthio group, an n-butylthio group, an n-pentylthio group, an n-hexylthio group, an i-propylthio group, an i-butylthio group, a sec-butylthio group, a t-butylthio group, an i-pentylthio group, a neopentylthio group, a t-pentylthio group, an i-hexylthio group, a cyclopropylthio group, a cyclobutylthio group, a cyclopentylthio group, a cyclohexylthio group, a cycloheptylthio group or a cyclooctylthio group or the like;

the acyl group is not only a formyl group but also an alkylcarbonyl group the alkyl portion of which is a lower alkyl group, as well as an arylcarbonyl group and may be exemplified by an acetyl group, a propionyl group, a butyryl group, a valeryl group, an isobutyryl group, an isovaleryl group, a pivaloyl group, a benzoyl group, a phthaloyl group or a toluoyl group or the like;

the lower alkoxycarbonyl group is an alkoxycarbonyl group the alkyl portion of which is a lower alkyl group and may be exemplified by a methoxycarbonyl group, an ethoxycarbonyl group, an n-propoxycarbonyl group, an n-butoxycarbonyl group, an n-pentoxycarbonyl group, an n-hexoxycarbonyl group, an i-propoxycarbonyl group, an i-butoxycarbonyl group, a sec-butoxycarbonyl group, a t-butoxycarbonyl group, an i-pentoxycarbonyl group, a neopentoxycarbonyl group, a t-pentoxycarbonyl group, an i-hexoxycarbonyl group, a cyclopropoxycarbonyl group, a cyclobutoxycarbonyl group, a cyclopentoxycarbonyl group, a cyclohexoxycarbonyl group, a cycloheptoxycarbonyl group, or a cyclooctoxycarbonyl group or the like;

the halogen atom is a fluorine atom, a chlorine atom, a bromine atom or an iodine atom;

the leaving group is a halogen atom, a trifluoromethanesulfonyloxy group, a p-toluenesulfonyloxy group or a methanesulfonyloxy group;

the substituent in the case where R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, X_{10}, X_{11}, X_{12}, X_{13}, or X_{14} is an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, an optionally substituted lower alkylthio group or an optionally substituted lower alkoxycarbonyl group may be exemplified by a halogen atom, a phenyl group optionally substituted by a halogen atom or a lower alkyl group or a cyclic alkyl group having 3 - 8 carbon atoms;

the ring as the 3- to 8-membered ring optionally formed by R_1 and R_2 taken together, the ring as the 3- to 8-membered ring optionally formed by X_5 and X_6 taken together, the ring as the 3- to 8-membered ring optionally formed by X_8 and X_9 taken together, the ring as the 3- to 8-membered ring optionally formed by X_{10} and X_{11} taken together, and the ring as the 3- to 8-membered ring optionally formed by X_{13} and X_{14} taken together are each a hetero ring containing at least one nitrogen atom as a hetero atom and may be exemplified by a pyrrole ring, a pyrazole ring, an imidazole ring, a triazole ring, an aziridine ring, an azetidine ring, a pyrrolidine ring, a piperidine ring, a piperazine ring, a morpholine ring, a thiomorpholine ring, an azepane ring or an azocane ring or the like;

the ring as the monocyclic or fused ring having 3 - 10 carbon atoms that is optionally formed by R_3 and R_4 taken together may be exemplified by a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring,

a cycloheptane ring, a cyclooctane ring, an indane ring or a tetralin ring or the like;

NX_5X_6, NX_8X_9, $NX_{10}X_{11}$, and $NX_{13}X_{14}$ may be exemplified by an amino group, a methylamino group, a benzylamino group, an ethylamino group, a dimethylamino group, an ethylmethylamino group, a pyrrolidine-1-yl group, a piperidine-1-yl group, a morpholine-4-yl group, an acetamido group, a benzamido group, an N-methylacetamide group, a benzamido group, a tert-butoxycarbonylamino group, an N-methyl-t-butoxycarbonyl-amino group, a pyrrole-1-yl group, a pyrazole-1-yl group, an imidazole-1-yl group, a triazole-1-yl group, an aziridine-1-yl group, an azetidine-1-yl group, a pyrrolidine-1-yl group, a piperidine-1-yl group, a piperazine-1-yl group, a morpholine-4-yl group or a thiomorpholine-4-yl group or the like;

$C(=O)X_7$ may be exemplified by a formyl group, a carboxyl group, an acetyl group, a propionyl group, a cyclobutyryl group, a methoxycarbonyl group, an ethoxycarbonyl group, a t-butoxycarbonyl group, a carbamoyl group, an N-methylcarbamoyl group, an N-ethylcarbamoyl group, an N,N-dimethylcarbamoyl group, an N-ethyl-N-methylcarbamoyl group, a pyrrolidinecarbonyl group, a piperidinecarbonyl group or a morpholinecarbonyl group or the like;

R_1 and R_2 are preferably a hydrogen atom;

R_3 and R_4 are preferably a hydrogen atom, a lower alkyl group having 1 - 3 carbon atoms or a monocyclic ring having 3 - 5 carbon atoms, with a hydrogen atom, a methyl group, an ethyl group or a cyclobutyl group being particularly preferred;

R_5 is preferably a hydrogen atom;

X_1, X_2, X_3, and X_4 are preferably a hydrogen atom, a halogen atom, a lower alkyl group having 1 - 3 carbon atoms or a lower alkoxy group having 1 - 3 carbon atoms, with a hydrogen atom, a fluorine atom, a chlorine atom, a methyl group, an ethyl group, a methoxy group, an ethyoxy group or an n-propoxy group being particularly preferred;

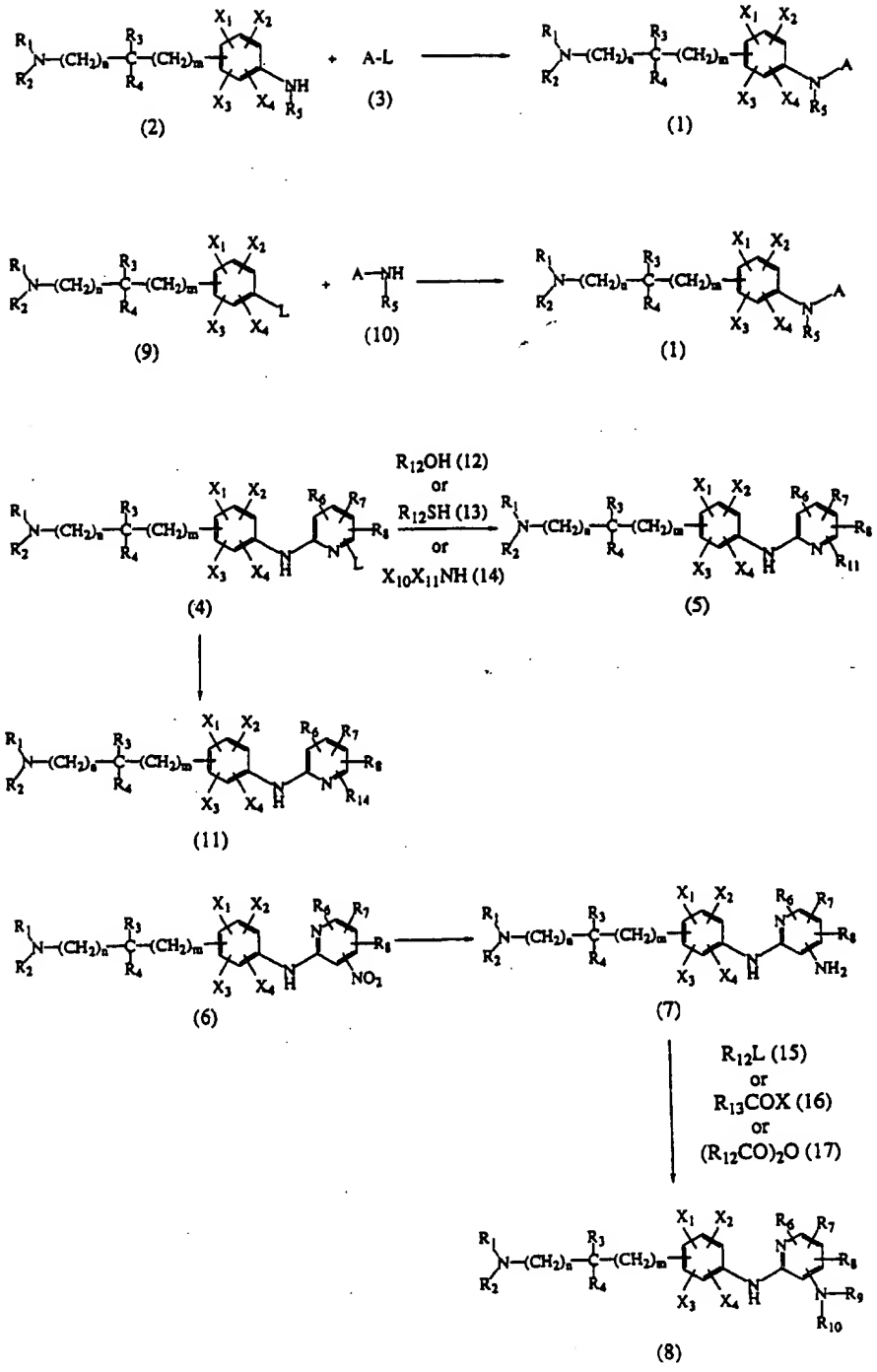
A is preferably an optionally substituted benzene or pyridine ring, and more preferred is a benzene or pyridine ring that is substituted by a nitro group, a lower alkyl group having 1 - 3 carbon atoms, a lower alkoxy group having 1 - 3 carbon atoms or a lower alkylthio group having 1 - 3 carbon atoms, with a 6-methoxy-3-nitrobenzene-2-yl group, a 6-methyl-3-nitropyridine-2-yl group, a 6-methoxy-3-nitro-pyridine-2-yl group or a 4-methylpyridine-2-yl group being particularly preferred;

m and n are such that if they are both zero, the substituents other than X_1, X_2, X_3, and X_4 are preferably meta-substituted on the benzene nucleus whereas if $m + n = 1$, the substituents other than X_1, X_2, X_3, and X_4 are preferably ortho- or para-substituted on the benzene nucleus.

[0021] Preferred compounds represented by the general formula (1) are 2-(3-aminomethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-3-ethyl-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-ethoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methylthio-3-nitropyridine, 2-(3-aminomethylphenylamino)-6-methyl-3-nitrobenzene, 2-(3-aminomethylphenylamino)-6-methoxy-3-nitrobenzene, 2-(3-aminomethyl-2-methylphenylamino)-6-methoxy-3-nitropyridine, 2-(4-aminoethylphenylamino)-6-methoxy-3-nitropyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-4-fluorophenylamino)-6-methoxy-3-nitro-pyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethyl-2-chlorophenylamino)-6-methoxy-3-nitropyridine, 2-(3-aminomethylphenylamino)-4-methylpyridine, 2-(3-(1-amino-1-methylethyl)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-ethoxyphenylamino)-4-methylpyridine, 2-(2-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-chlorophenylamino)-4-methylpyridine, 2-(3-(1-amino-cyclobutyl)phenylamino)-4-methylpyridine, 2-(4-aminoethylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chlorophenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-(n-propoxy)phenylamino)-4-methylpyridine, 2-(3-aminomethyl-4-chloro-2-ethoxyphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-ethoxy-4-methylphenylamino)-4-methylpyridine, 2-(3-aminomethyl-2-methoxyphenylamino)-4-methylpyridine and 2-(3-aminomethyl-2-(i-propoxy)phenylamino)-4-methylpyridine.

[0022] In addition to the compounds represented by the general formula (1), the present invention also encompasses their possible tautomers, stereoisomers, optionally active forms and mixtures thereof.

[0023] The compounds of the invention which are represented by the general formula (1) may typically be synthesized by the following schemes:



[0024] The compound represented by the general formula (1) can be synthesized by reacting a compound of the general formula (2), used as a starting material, with a compound of the general formula (3).

[0025] In the general formulas (1), (2) and (3), R_1, R_2, R_3, R_4, R_5, X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8, X_9, A, L, n and m

each have the same meanings as defined above.

[0026] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (2) with the compound of the general formula (3) in the presence of a base such as potassium carbonate, triethylamine, diisopropylethylamine, potassium t-butoxide or sodium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphophinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or 1,4-dioxane, at a temperature between room temperature and the boiling point of the reaction mixture. Preferably synthesis can be made by performing the reaction in the presence of triethylamine or diisopropylethylamine in dimethylformamide at 60°C or by performing the reaction in the presence of potassium carbonate, potassium t-butoxide or sodium t-butoxide, with a palladium catalyst and a ligand diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl added, in acetonitrile or toluene at a temperature between 80°C and the boiling point of the reaction mixture.

[0027] The compound represented by the general formula (1) can also be synthesized by reacting a compound of the general formula (9), used as a starting material, with a compound of the general formula (10).

[0028] In the general formulas (1), (9) and (10), R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, R_5, A, L, m and n each have the same meanings as defined above.

[0029] Stated more specifically, the compound represented by the general formula (1) can be synthesized by reacting the compound of the general formula (9) with the compound of the general formula (10) in the presence of a base such as potassium carbonate, triethylamine, potassium t-butoxide or sodium t-butoxide, preferably in the presence of potassium t-butoxide, with a metal catalyst such as copper, palladium or nickel and a ligand such as diphenylphosphinoethane, diphenylphosphinopropane, diphenylphosphinoferrocene or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl being added as required, preferably a palladium catalyst and a ligand diphenylphosphinoferrocene being added, in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or dimethylformamide, tetrahydrofuran, acetonitrile, toluene or dioxane, preferably in toluene, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at 80°C.

[0030] Among the compounds represented by the general formula (1), one which is represented by the general formula (5) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$ can also be synthesized starting with a compound of the general formula (4) with the leaving group attached.

[0031] In the general formulas (4), (5), (12), (13) and (14),

R_1, R_2, R_3, R_4, X_1, X_2, X_3, X_4, L, m and n each has the same meanings as defined above;
R_6 is an electron withdrawing group such as a nitro group, a cyano group, a trifluoromethyl group or $C(=O)X_7$;
R_7 and R_8 are each a hydrogen atom, a halogen atom, a nitro group, a cyano group, a trifluoromethyl group, a hydroxyl group, a lower alkoxy group, a lower alkyl group, a lower alkylthio group, NX_5X_6 or $C(=O)X_7$;
where X_5, X_6, and X_7 each has the same meanings as defined above;
R_{11} is a lower alkoxy group, a lower alkylthio group or $NX_{10}X_{11}$;
R_{12} and X_{10} are each a lower alkyl group;
X_{11} is a hydrogen atom or a lower alkyl group.

[0032] Stated more specifically, the compound represented by the general formula (5) can also be synthesized from the compound of the formula (4) by desirably reacting it with a corresponding compound of the general formula (12), (13) or (14) in the presence of a base such as triethylamine or sodium hydride in a solvent inert to the reaction such as dimethylformamide, tetrahydrofuran or acetonitrile at a temperature between room temperature and the boiling point of the reaction mixture.

[0033] Among the compounds represented by the general formula (1), one which is represented by the general formula (11) where A is an optionally substituted pyridine ring and one of the substituents present is a lower alkyl group can also be synthesized by decarboxylation a compound obtained by performing a nucleophilic substitution on a lower alkyl dicarbonate corresponding to a compound of the general formula (4) with the leaving group attached.

[0034] In the general formulas (4) and (11),

R_1, R_2, R_3, R_4, R_6, R_7, R_8, X_1, X_2, X_3, X_4, m and n each have the same meanings as defined above; and
R_{14} is a lower alkyl group.

[0035] Stated more specifically, the compound represented by the general formula (11) can also be synthesized from the compound of the general formula (4) by desirably reacting it with a corresponding lower alkyl dicarbonate in the presence of a base such as sodium hydride in a solvent inert to the reaction as exemplified by dimethylformamide, tetra-

hydrofuran or acetonitrile, preferably in dimethylformamide, at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature and thereafter subjecting the product to reaction in aqueous sulfuric acid at the boiling point of the reaction mixture.

[0036] Examples of the lower alkyl dicarbonate include dimethyl malonate, diethyl malonate, diethyl methylmalonate, diethyl ethylmalonate, diethyl n-propylmalonate, diethyl i-propylmalonate, diethyl n-butylmalonate, diethyl i-butylmalonate, diethyl t-butylmalonate, diethyl n-pentylmalonate and so forth.

[0037] Among the compounds represented by the general formula (1), one which is represented by the general formula (7) where A is an optionally substituted pyridine ring and one of the substituents present is an amino group can also be synthesized by reducing the nitro group in the corresponding general formula (6).

[0038] In the general formulas (6) and (7),

R_1, R_2, R_3, R_4, m and n each have the same meanings as defined above;
R_6, R_7, and R_8 are each a hydrogen atom, a halogen atom, a trifluoromethyl group, a hydroxyl group, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, NX_5X_6 or COX_7;
where X_5, X_6, and X_7 each have the same meanings as defined above;
X_1, X_2, X_3, and X_4 are each a hydrogen atom, a halogen atom, a phenyl group optionally substituted with a halogen atom and/or a lower alkyl group, a hydroxyl group, an optionally substituted lower alkyl group, an optionally substituted lower alkoxy group, NX_5X_6 or COX_7;
where X_5, X_6, and X_7, each have the same meanings as defined above.

[0039] Stated more specifically, the compound represented by the general formula (7) can also be synthesized by subjecting the compound of the general formula (6) to catalytic reduction in a solvent inert to the reaction as exemplified by ethanol, methanol, ethyl acetate, acetic acid or 1,4-dioxane, preferably in ethanol or methanol, in a hydrogen atmosphere at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature, with palladium-carbon, Raney nickel or platinum oxide used as a catalyst, or by performing reduction using nickel (II) chloride or sodium borohydride, so as to reduce the nitro group.

[0040] Among the compounds represented by the general formula (1), one which is represented by the general formula (8) where A is an optionally substituted pyridine ring and one of the substituents present is NR_9R_{10} can also be synthesized with a compound of the general formula (7) used as a starting material.

[0041] In the general formulas (7), (8), (15), (16) and (17),

R_1, R_2, R_3, R_4, R_6, R_7, R_8, R_{12}, X_1, X_2, X_3, X_4, L, m and n each have the same meanings as defined above;
R_9 is a hydrogen atom or a lower alkyl group;
R_{10} is a lower alkyl group, an acyl group or a lower alkoxycarbonyl group;
R_{13} is a lower alkyl group optionally substituted by a phenyl group; and
X is a halogen atom.

[0042] Stated more specifically, the compound represented by the general formula (8) can also be synthesized from the compound of the general formula (7) by desirably reacting it with a corresponding compound of the general formula (15), (16) or (17) in the presence of a base such as triethylamine or potassium carbonate in a solvent inert to the reaction at a temperature between room temperature and the boiling point of the reaction mixture, preferably at room temperature.

[0043] If in the process of synthesizing the compounds represented by the above formulas (1), (5), (7), (8) and (11), a protective group is necessary for the primary or secondary amino group, they are first protected either with a suitable resin or with one of the appropriate protective groups described in Green and Wuts, "PROTECTIVE GROUPS IN ORGANIC SYNTHESIS", 2nd Edition, John Wiley & Sons Inc., p. 309, 1991, and thereafter the respective reactions are performed. If necessary, the protected groups may be subjected to a deprotecting reaction. Examples of the amino protecting group include a t-butoxycarbonyl group, a trifluoroacetyl group and so forth.

[0044] The amino protecting reaction such as t-butoxycarbonylation may be performed by reacting the respective compound with di-t-butyl dicarbonate in a solvent inert to the reaction as exemplified by an alcohol such as methanol, ethanol or i-propanol or methylene dichloride, dimethyl-formamide or 1,4-dioxane in the presence of an organic base such as triethylamine or 4-dimethylamiopyridine at a temperature between 0°C and room temperature.

[0045] The amino protecting reaction may also be performed with a Wang resin by reacting the respective compound with a 4-nitrophenyloxycarbonyl-Wang resin (Tetrahedron Lett., 37, 937-940 (1996)) in a solvent inert to the reaction as exemplified by methylene chloride, dimethylformamide or 1,4-dioxane in the presence of an organic base such as 4-methylmorpholine, triethylamine or 4-dimethylaminopyridine at a temperature between 0°C and room temperature.

[0046] If the protecting group is a t-butoxycarbonyl group or the Wang resin mentioned above, a reaction for deprotecting the amino group is preferably performed in a solvent inert to the reaction as exemplified by methanol, ethanol,

1,4-dioxane or methylene chloride or without using any solvent at all, with the aid of a deprotecting agent such as trifluoroacetic acid, hydrochloric acid, sulfuric acid or methanesulfonic acid at a temperature between 0°C and room temperature, with the use of anhydrous conditions, room temperature and trifluoroacetic acid being particularly preferred.

[0047] If the compounds of the invention which are represented by the general formula (1) have asymmetric carbons in their structure, the pure forms of their stereoisomers and optically active forms can be obtained by known techniques in the art, such as chromatography on optical isomer separating columns and fractional crystallization.

[0048] Pharmaceutically acceptable salts of the compounds of the invention which are represented by the general formula (1) may be of any types as long as they are pharmaceutically acceptable salts and typical examples include salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, hydrobrobromic acid and hydroiodic acid, salts with organic acids such as formic acid, acetic acid, oxalic acid and tartaric acid, salts with alkali metals such as sodium and potassium, and salts with alkaline earth metals such as calcium and magnesium.

[0049] The compounds of the invention or salts thereof may be formulated with suitable excipients, adjuvants, lubricants, antiseptics, disintegrators, buffering agents, binders, stabilizers, wetting agents, emulsifiers, coloring agents, flavoring agents, fragrances, etc. to form tablets, granules, subtilized granules, powders, capsules, syrups, elixirs, suspensions, emulsions, injections, etc. for oral or parenteral administration. When the cerebrovascular diseases to be treated are in a hyperacute phase (immediately after the stroke), an acute phase (from the stroke to 2 or 3 days later) or in a subacute phase (2 or 3 days up to 2 weeks after the stroke), administration is effected primarily by intramuscular or intravenous injection. In addition, oral administration may be performed in a chronic phase (the third week after stroke and onward) if the patient admits ingestion.

[0050] The compounds of the invention or salts thereof may be administered in doses that vary with the physical constitution of the patient, his or her age, physical condition, the severity of the disease, the time of lapse after the onset of the disease and other factors; typical daily doses range from 0.5 to 5 mg/body for oral administration and from 1 to 10 mg/body for parenteral administration. It should generally be noted that even if the same dose is administered, the plasma concentration may sometimes vary considerably between patients; hence, an optimal dose of the drug should ideally be determined for each patient on the basis of a monitored plasma concentration of the drug.

[0051] If the compounds of the invention or salts thereof are to be formulated as preparations for internal application, lactose, sucrose, sorbitol, mannitol, starches such as potato starch or corn starch, starch derivatives and common additives such as cellulose derivatives or gelatin are suitably used as vehicles, with lubricants such as magnesium stearate, carbowaxes and polyethylene glycol being optionally added concurrently; the resulting mixtures may be formulated in the usual manner into granules, tablets, capsules or other forms suitable for internal application.

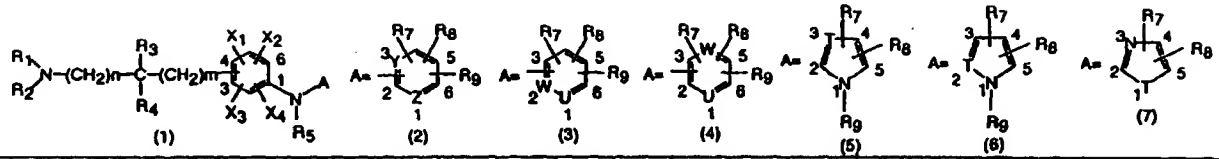
[0052] If the compounds of the invention or salts thereof are to be formulated as aqueous preparations, effective amounts of the principal ingredients may be dissolved in distilled water for injection, with antioxidants, stabilizers, dissolution aids, buffering agents, preservatives, etc. added as required and, after complete solutions are formed, they are filtered, filled into ampules and sealed in the usual manner and sterilized by a suitable medium such as high-pressure vapor or dry heat so as to prepare injections.

[0053] If the compounds of the invention or salts thereof are to be formulated as lyophilized preparations, aqueous solutions having the principal ingredients dissolved in distilled water for injection may be freeze-dried in the usual manner; depending on the need, excipients that provide for easy lyophilization, such as sugars (e.g. lactose, maltose and sucrose), sugar alcohols (e.g. mannitol and inositol), glycine and the like, may be added before freeze-drying is performed in the usual manner to make the intended preparations.

Examples

[0054] Lists of the compounds prepared in the Examples of the invention are given in Tables 1 - 37 below.

Table 1

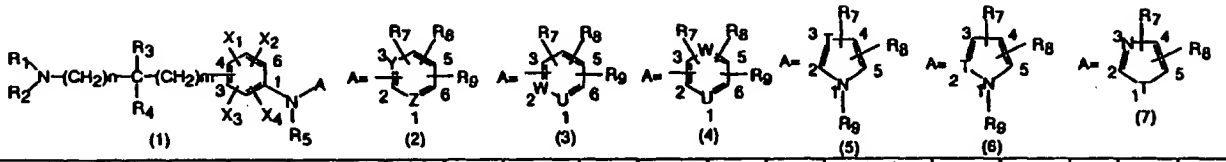


Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of ★	R_1	R_2	n	R_3	R_4	m	R_5	salt
1	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
2	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
3	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
4	(2)	CR_6	N	NO_2	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
5	(2)	CR_6	N	NHMe	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
6	(2)	CR_6	N	NHMe	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	
7	(2)	CR_6	N	NHEt	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
8	(2)	CR_6	N	NHEt	2	4-H	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
9	(2)	CR_6	N	H	2	4-H	5-NO_2	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
10	(2)	CR_6	N	H	2	4-H	5-NO_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
11	(2)	CR_6	N	H	2	4-H	5-NH_2	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
12	(2)	CR_6	N	H	2	4-H	5-NH_2	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
13	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
14	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
15	(2)	CR_6	N	NO_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★ : W = $-(CH_2)_m-C(R_3)(R_4)-(CH_2)_n-N(R_1)(R_2)$

Table 2



Ex. No.	A	Y	Z	R_6	Substitution position of A	R_7*1	R_8*1	R_9*1	X_1*2	X_2*2	X_3*2	X_4*2	Substitution position of W	R_1	R_2	n	R_3	R_4	m	R_5	salt
16	(2)	CR_6	N	NH_2	2	4-Me	5-H	6-H	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
17	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
18	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
19	(2)	CR_6	N	NH_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
20	(2)	CR_6	N	NH_2	2	4-H	5-H	6-OMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	2HCl
21	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
22	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-OMe	5-H	6-H	3	H	H	0	H	H	0	H	HCl
23	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
24	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	H	H	0	H	H	0	H	HCl
25	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	$CO_2{}^tBu$	H	0	Indan-2-yl		0	H	
26	(2)	CR_6	N	NO_2	2	4-H	5-H	6-OMe	2-H	4-Et	5-H	6-H	3	H	H	0	Indan-2-yl		0	H	HCl
27	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
28	(2)	CR_6	N	NO_2	2	4-H	5-H	6-Cl	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl
29	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHMe	2-H	4-H	5-H	6-H	3	$CO_2{}^tBu$	$CO_2{}^tBu$	0	H	H	0	H	
30	(2)	CR_6	N	NO_2	2	4-H	5-H	6-NHMe	2-H	4-H	5-H	6-H	3	H	H	0	H	H	0	H	HCl

*1:Numerals represent substitution positions in the structural formulas of (2)-(7) employed.
*2:Numerals represent substitution positions on the benzene ring.

★: W = $-(CH_2)_m-C(R_3)(R_4)-(CH_2)_n-N(R_1)(R_2)$